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American Journal of Diseases of Children

Vol. 12 SEPTEMBER, 1916 No. 3

SCARLET FEVER, MORBIDITY AND FATALITY

BASED ON SEVERAL MILLION CASES *

H. H. DONNALLY, A.M., M.D.
WASHINGTON, D. C.

Certain families are more susceptible to scarlet fever than others. Physicians in active practice in contagious hospitals and elsewhere are familiar with this fact, because all the children in some families have the disease, whereas the rule is for but one or two of a number of brothers and sisters exposed to have scarlet fever. Besides this, physicians know that certain types of children—fat, flabby, overnourished and pasty children—bear the disease badly, and this gives rise to the knowledge that there is a variation in individual susceptibility. Could these differences in family and individual susceptibilities account for differences in fatality between different small epidemics of scarlet fever? Suppose that large collections of cases in various parts of the world were studied and compared, would it be found, with all types of individuals and families included, that scarlet fever after all was a fairly uniform disease, attacking year in and year out an average number of children, of whom an average number could be regularly expected to die in a fairly uniform proportion?

A study of these and similar questions by means of board of health statistics was suggested to me by Dr. John Howland for the epidemic diseases of childhood. Starting out with all the reportable diseases, it was found that scarlet fever was the one which admitted of such investigation with the greatest satisfaction, because it is and has been for some time generally well reported and has undergone little change in treatment, and also because it can usually be readily diagnosticated.[1] Diphtheria has had its specific treatment, which has tremendously influenced the figures. Measles, whooping cough and chickenpox are often so mild and so matter of course that a good proportion of cases are passed through without a call for a medical attendant, and remain unknown to the authorities. Difficulties of nice diagnosis rule out

* Submitted for publication May 22, 1916.

1. The error in diagnosis in New York City in 1914 was 1.6 per cent.

cerebrospinal meningitis from such a study, and infantile paralysis is too recent a disease in health office figures to make its study worth while.

Notification of contagious diseases is not a very old requirement and has but recently become general. Its value has become widely recognized, and severe penalties for failure by a physician to report a case of scarlet fever and constant watchfulness on the part of the authorities have resulted in adequate notifications in the main. The value of a study such as the present one is dependent upon the com-

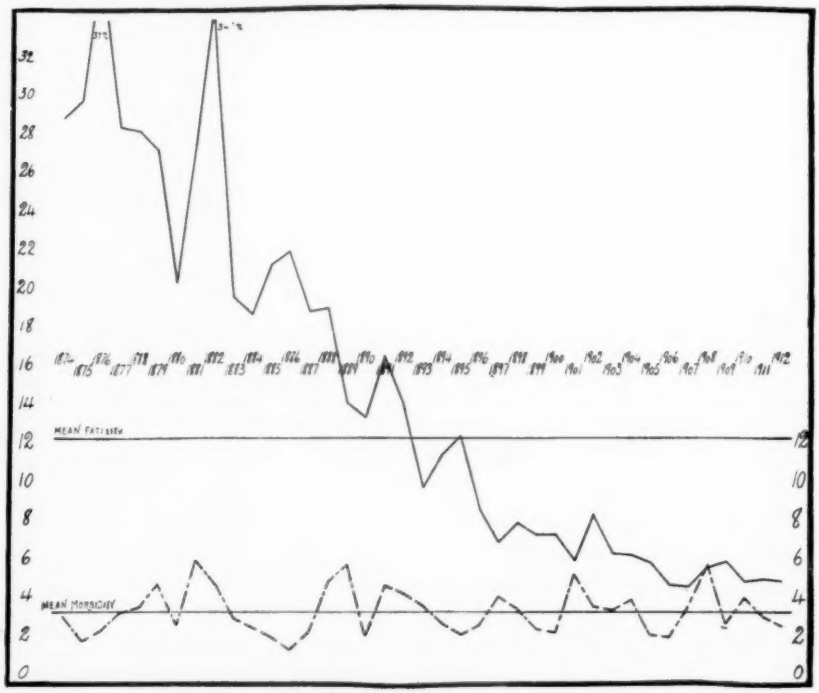

Fig. 1.—Morbidity and case fatality in New York for thirty-nine years, from 1874 to 1912, there being 229,071 cases, with 27,889 deaths, a case fatality of 12.2 per cent., and a morbidity rate of 3.2 per 1,000 population. The solid lines in Figures 1 to 12, inclusive, show the number of deaths per 100 cases; the broken line shows the number of cases per 1,000 population.

pleteness of the work of practicing physicians in making these reports. We know that all cases are not reported. With scarlet fever the very mild cases, which are unrecognized, and the very severe ones, in which the patients die without scarlet fever being given as the cause of death, balance to some degree, so that it is believed that the fatality figures obtained for this study give an approximately accurate idea of true conditions. Some health officials in their reports twenty-five or thirty

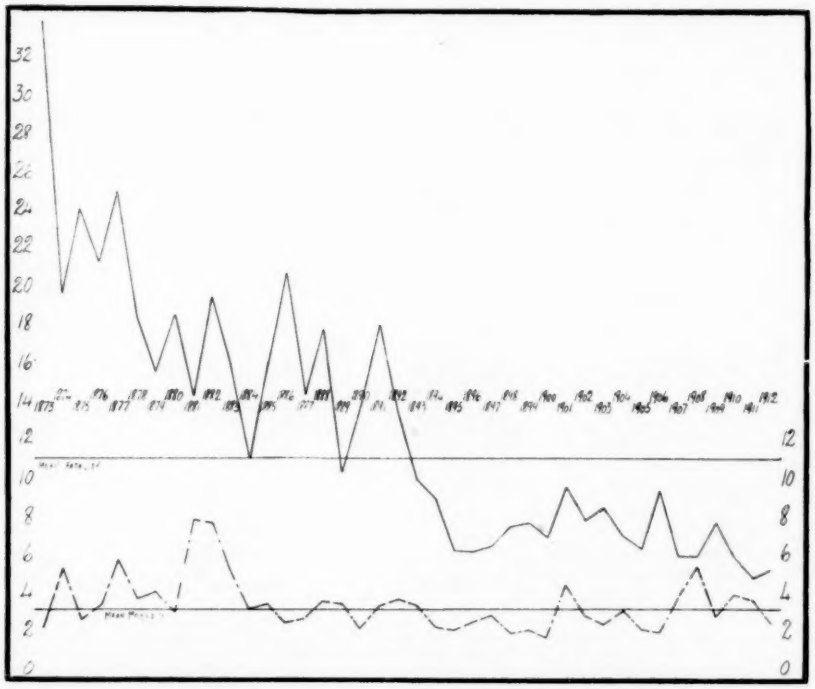

Fig. 2.—Morbidity and case fatality in Brooklyn for forty years, from 1873 to 1912, there being 122,928 cases with 13,492 deaths, a case fatality of 11 per cent., and a morbidity rate of 3.2 per 1,000 population.

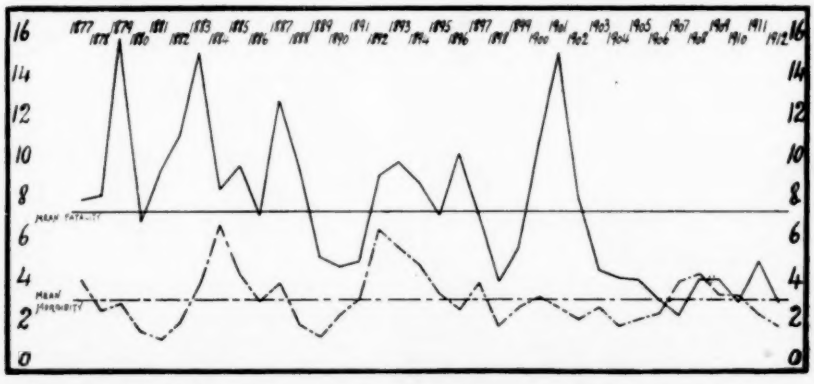

Fig. 3.—Morbidity and case fatality in Boston for thirty-six years, from 1877 to 1912, there being 52,246 cases and 3,755 deaths, a case fatality of 7.2 per cent. and a morbidity rate of 2.9 per 1,000 population.

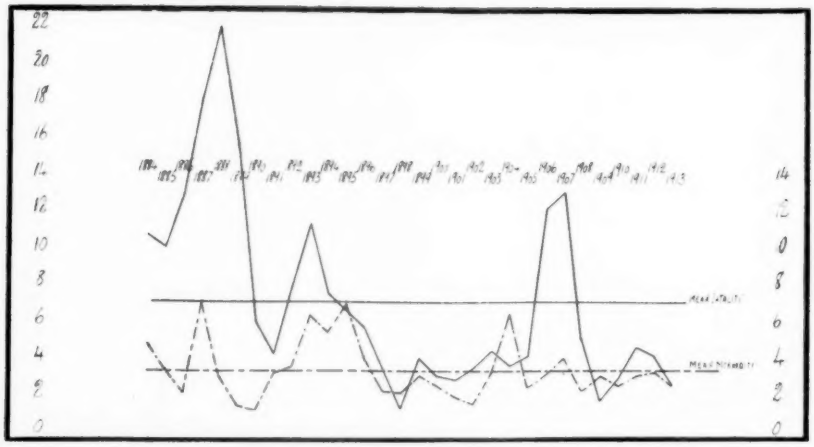

Fig. 4.—Morbidity and case fatality in Providence for thirty years, from 1884 to 1913, there being 16,135 cases with 1,141 deaths, a case fatality of 7.1 per cent. and a morbidity rate of 3.2 per 1,000 population.

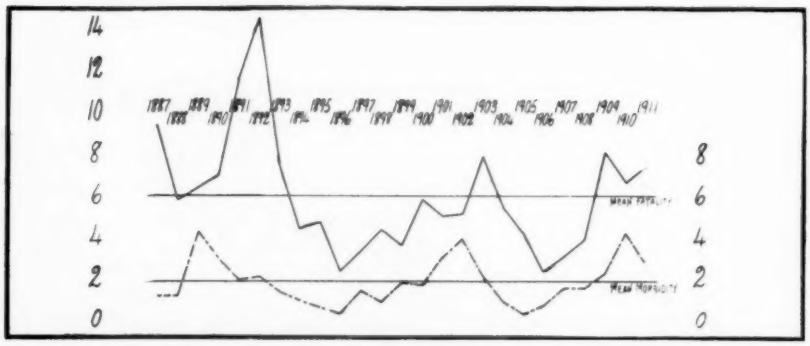

Fig. 5.—Morbidity and case fatality in St. Louis for twenty-five years, from 1887 to 1911, there being 27,213 cases with 1,625 deaths, a case fatality of 6 per cent. and a morbidity rate of 1.9 per 1,000 population.

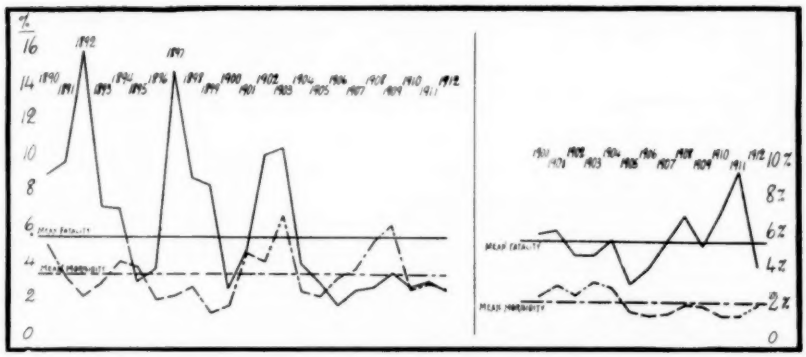

Fig. 6.—Morbidity and case fatality: at the left, in Nuremberg for twenty-three years, from 1890 to 1912, there being 18,657 cases with 1,003 deaths, a case fatality of 5.4 per cent. and a morbidity rate of 3.3 per 1,000 population; at the right, in Philadelphia for thirteen years, from 1900 to 1912, there being 35,204 cases with 1,876 deaths, a case fatality of 5.2 per cent. and a morbidity rate of 1.9 per 1,000 population.

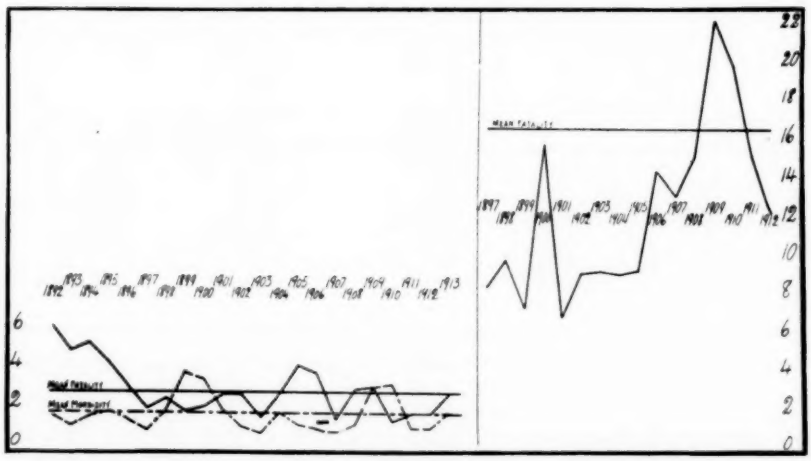

Fig. 7.—Morbidity and case fatality: at the left, in Washington, D. C., for twenty-two years, from 1892 to 1913, there being 9,476 cases with 238 deaths, a case fatality of 2.5 per cent. and a morbidity rate of 1.5 per 1,000 population; at the right, in Japan for sixteen years, from 1897 to 1912, there being 8,882 cases with 1,452 deaths, a case fatality of 16.3 per cent.

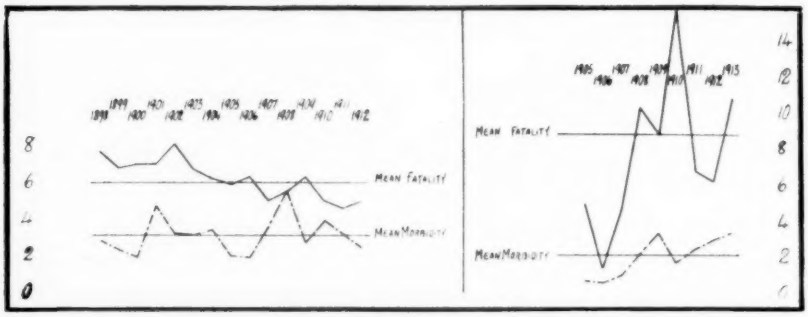

Fig. 8.—Morbidity and case fatality: at the left, in Greater New York, for fifteen years, from 1898 to 1912, there being 192,710 cases with 11,576 deaths, a case fatality of 6 per cent. and a morbidity rate of 3.1 per 1,000 population; at the right, in Montreal for nine years, from 1905 to 1913, there being 7,820 cases with 684 deaths, a case mortality of 8.7 per cent. and a morbidity rate of 2.1 per 1,000 population.

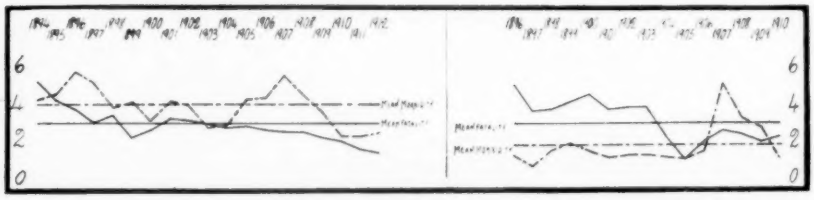

Fig. 9.—Morbidity and case fatality: at the left, in London, for nineteen years, from 1894 to 1912, there being 335,949 cases with 9,921 deaths, a case fatality of 3 per cent. and a morbidity rate of 3.9 per 1,000 population; at the right, in Paris, for fifteen years, from 1896 to 1910, there being 72,189 cases with 2,142 deaths, a case fatality of 3 per cent. and a morbidity of 1.8 per 1,000 population.

years ago spoke confidently on the adequacy of registration as far as scarlet fever cases were concerned. Even at the present day notification is inadequate in some countries. It is curious that such a state as Prussia, with its great complexity of laws, has had no compulsory notification law. The law in operation dates back to 1835 and provides that notification shall be made when scarlet fever is "particularly numerous or particularly malignant." For my purposes, therefore, the figures from Prussia are useless, no attempt being made there to report all cases. In Norway reporting has been excellent and the writer has brought certain tables in Johannessen's classic work[2] down to date.

Morbidity and fatality rates are based on the number of cases and deaths reported during a calendar year, and not infrequently the figures of epidemics have been broken into, but it is believed that the treatment of numbers of years together has compensated for this.

In all, something over seven million cases have been collected, but for various

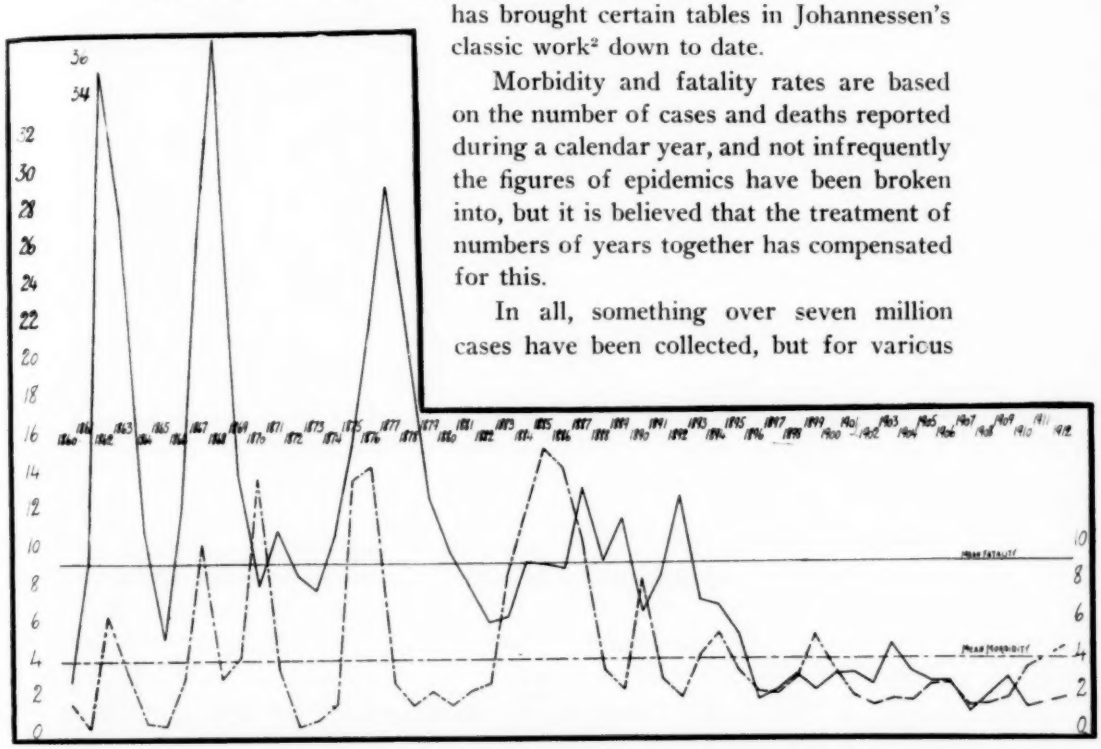

Fig. 10.—Morbidity and case fatality in Christiania for fifty-three years, from 1860 to 1912, there being 26,993 cases with 2,433 deaths, a case fatality of 9 per cent. and a morbidity rate of 3.8 per 1,000 population.

reasons some of these have had to be put aside, only those being retained concerning which it was believed that cases and deaths were well reported. Among approximately 2,000,000 cases there were 104,500 deaths, which gives a case fatality of 5¼ per cent., while the morbidity rate was 3.9, that is, about four persons in each 1,000 inhabi-

2. Johannessen: Die epidemische Verbreitung des Scharlachfiebers in Norwegen, Kristiania, 1884.

TABLE 1.—MORBIDITY AND CASE FATALITY—

Place	Period as a Whole						
	Time	Number of Years	Annual Populations (Aggregate)	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
Eight American cities	1873-1913	41	177,047,815	2.8	500,093	50,700	10.1
Paris	1896-1910	15	40,070,803	1.8	72,189	2,142	3.0
Nuremberg	1890-1913	22	5,650,000	3.3	18,657	1,003	5.4
Norway	1867-1910	44	.....	2.5	233,587	18,556	7.9
Norway	(1880-1910)	(31)	(11,689,508)	(2.5)	(162,592)	(9,349)	
Russian Empire	1893-1910	14	.....	2.0	2,793,453	845,641	22.3
England and Wales	1892-1911	17	268,253,879	4.6	1,231,018	41,192	3.3
Prussia	1902-1912	11	.....	.....	787,476	59,079	7.5
Italy	1888-1910	23	.....	.....	428,541	93,094	21.7
Japan	1897-1912	16	.....	.....	8,882	1,452	16.3
Grand total			.....	.....	7,073,806	.....	....
Total, exclusive of Russia, Japan, Italy and Prussia			.....	.....	2,055,544	113,593	5.5
Total, exclusive of Russia, Japan, Italy and Prussia, also Norway between 1867 and 1879			502,712,005	3.9	1,984,549	104,386	5.26

TABLE 2.—MORBIDITY AND CASE FATALITY OF—

Place	Period as a Whole						
	Time	Number of Years	Annual Populations (Aggregate)	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
Boston	1877-1912	36	18,051,007	2.9	52,246	3,755	7.2
Providence	1884-1913	30	5,105,611	3.2	16,135	1,141	7.1
New York (old)	1874-1912	39	71,852,353	3.2	229,071	27,889	12.2
Brooklyn	1873-1912	40	38,492,166	3.2	122,928	13,492	11.0
St. Louis	1887-1911	25	14,456,089	1.9	27,213	1,625	6.0
Philadelphia	1900-1912	13	18,862,594	1.9	35,204	1,876	5.3
Washington	1892-1913	22	6,505,482	1.46	9,476	238	2.5
Montreal	1905-1913	9	3,722,423	2.1	7,820	684	8.7
Total	.....	.....	177,047,815	2.82	500,093	50,700	10.1

—OF SCARLET FEVER IN VARIOUS COUNTRIES

Year of Maximum Fatality					Year of Minimum Fatality				
Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases	Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
....	.....	.....	.....	....	....	.....	.....	.....	....
1896	1.3	3,283	170	5.1	1905	1.1	2,952	43	1.1
1892	2.1	321	51	15.8	1906	3.1	941	15	1.6
1877	1.8	7,850	1,183	15.1	1910	1.7	4,092	80	2.0
1904	2.3	323,488	126,904	39.0	1901	2.2	294,268	34,127	11.5
1894	4.3	53,045	2,514	4.7	1911	5.4	104,617	1,871	1.8
1909	.....	91,512	8,455	9.2	1911	.....	80,660	5,114	6.4
1888	.....	4,532	9,050	200.0(!)	1909	.....	32,010	2,703	8.4
1909	.....	1,537	337	22.0	1901	.....	46	3	6.5

—SCARLET FEVER IN EIGHT AMERICAN CITIES

Year of Maximum Fatality					Year of Minimum Fatality				
Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases	Year	Cases per 1,000 Pop.	Cases	Deaths	Deaths per 100 Cases
1879	2.7	951	149	15.7	1907	3.8	2,359	49	2.1
1888	2.9	361	79	21.9	1898	2.0	322	4	1.2
1876	2.2	2,406	891	37.0	1907	3.7	9,389	421	4.5
1873	2.1	930	314	33.8	1911	3.6	6,136	295	4.8
1892	2.1	1,056	153	14.5	1896	0.4	252	6	2.4
1911	1.2	1,928	179	9.3	1905	1.4	1,992	57	2.9
1892	1.3	338	20	5.9	1910	3.0	1,001	11	1.1
1910	1.7	756	118	15.6	1906	0.6	210	3	1.4
....	.....	.....	.....	....	....	.....	.....	.....	....

TABLE 3.—Morbidity Rates in Calendar Years, Showing—

Place	1873	1874	1875	1876	1877	1878	1879	1880	1881	1882	1883	1884	1885	1886	1887	1888	1889	1890
New York (old)	....	3.0	1.7	2.2	3.1	3.4	4.6	2.5	5.8	4.6	2.9	2.4	1.9	1.2	2.1	4.7	5.6	1.9
Brooklyn	2.1	5.3	2.6	3.3	5.7	5.7	4.0	3.0	7.8	7.6	5.1	3.1	3.4	2.4	2.6	3.5	3.4	2.1
Boston	....	....	....	....	3.9	2.4	2.7	1.4	1.0	1.8	3.7	6.5	4.2	2.8	3.7	1.7	1.1	2.1
Providence	....	....	....	....	....	....	...	...	...	...	...	4.7	3.2	2.0	6.9	2.9	1.3	1.0
St. Louis	....	....	....	....	....	....	...	...	...	...	...	...	...	...	1.2	1.2	4.2	3.9
Montreal	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Philadelphia	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Washington	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Nuremberg	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	4.0
Christiania	0.6	1.5	13.4	14.1	2.6	1.4	2.1	1.4	2.1	2.5	8.2	11.6	15.0	14.0	10.0	3.3	2.2	8.1
Greater New York	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Paris	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
London	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Norway	1.7	1.0	3.0	7.1	4.4	2.7	2.3	2.4	3.1	4.6	4.3	3.1	4.1	5.6	4.8	3.7	2.7	3.7
England and Wales	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Russia	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...

TABLE 4.—Case Fatality in Calendar Years, Showing—

Place	1873	1874	1875	1876	1877	1878	1879	1880	1881	1882	1883	1884	1885	1886	1887	1888	1889	1890
New York (old)	....	28.8	29.7	37.0	28.3	28.1	27.1	20.3	27.4	34.7	19.5	18.6	21.2	21.9	18.7	18.9	14.0	13.2
Brooklyn	23.8	19.6	24.0	21.2	24.9	18.3	15.6	18.6	14.3	19.4	15.9	11.0	15.9	20.7	14.4	17.8	10.2	13.7
Boston	....	....	....	....	7.8	8.0	15.7	6.6	9.1	10.9	15.0	8.3	9.4	7.0	12.6	9.2	5.0	4.5
Providence	....	....	....	....	....	....	...	...	...	...	...	7.0	9.9	12.7	18.0	21.9	15.4	5.9
St. Louis	....	....	....	....	....	....	...	...	...	...	...	...	...	...	9.4	5.8	6.4	7.0
Montreal	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Philadelphia	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Washington	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Nuremberg	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	4.1	8.9
Christiania	7.5	10.4	15.2	21.7	20.0	20.4	12.4	9.6	7.8	5.8	6.1	9.0	8.9	8.7	12.9	9.1	11.3	6.4
Greater New York	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Paris	....	....	..	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
London	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Norway	12.6	12.3	13.2	13.7	15.1	14.3	14.0	12.7	14.5	12.9	9.4	8.1	6.9	7.5	...	6.3	6.0	6.0
England and Wales	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Russia	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...
Japan	....	....	....	....	....	....	...	...	...	...	...	...	...	...	...	...	...	...

—Number of Cases of Scarlet Fever Per 1,000 Population

1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910	1911	1912	1913	Aver. %
4.5	4.1	3.3	2.6	2.0	2.5	4.0	3.4	2.3	2.1	5.1	3.5	3.3	3.8	2.0	1.9	3.7	5.6	2.6	4.0	3.0	2.5	...	3.2
3.2	3.6	3.3	2.2	2.0	2.4	2.8	1.9	2.0	1.6	4.3	2.8	2.3	3.0	2.1	1.9	3.7	5.3	2.7	3.9	3.6	2.4	...	3.2
2.9	6.3	5.4	4.6	3.2	2.4	3.7	1.6	2.5	3.0	2.5	1.9	2.5	1.6	1.9	2.2	3.8	4.2	3.2	3.1	2.2	1.6	...	2.9
3.0	3.4	6.2	5.3	6.8	3.9	2.1	2.0	2.9	2.4	1.8	1.4	3.1	6.3	2.3	3.0	3.9	2.1	2.9	2.4	2.9	3.1	2.4	3.2
2.0	2.1	1.4	1.0	0.7	0.4	1.4	0.9	1.8	1.7	3.0	3.9	2.2	1.0	0.4	0.8	1.6	1.6	2.3	4.2	2.8	...	...	1.9
...	...	...	...	...	...	...	...	...	...	...	...	...	...	0.7	0.6	1.0	2.1	3.3	1.7	2.4	2.7	3.3	2.1
...	...	...	...	...	...	...	...	...	2.2	2.8	2.3	3.0	2.7	1.4	1.2	1.3	1.8	1.7	1.2	1.2	1.8	...	1.9
...	1.3	0.8	1.3	1.5	1.1	0.6	1.6	3.5	3.2	1.7	0.8	0.5	1.5	0.9	0.7	0.5	0.9	2.8	3.0	0.8	0.8	1.6	1.5
3.2	2.1	2.8	4.0	3.7	1.9	2.1	2.6	1.2	1.6	4.5	4.0	6.6	2.4	2.1	3.1	3.6	5.1	6.1	2.5	2.8	2.5	...	3.3
2.8	1.8	4.0	5.2	3.2	2.1	2.0	2.8	5.1	3.1	1.9	1.4	1.7	1.6	2.4	2.5	1.3	1.4	1.7	3.3	...	4.4	...	3.8
..	...	...	...	...	...	...	2.8	2.3	1.9	4.7	3.2	3.1	3.4	2.0	1.9	3.6	5.5	2.7	3.9	3.1	2.4	...	3.1
..	...	...	...	...	1.3	0.7	1.5	1.9	1.5	1.2	1.3	1.3	1.2	1.1	1.5	5.1	3.3	2.8	1.1	...	...	...	1.8
...	...	...	4.2	4.5	5.7	5.1	3.8	4.1	3.1	4.1	3.9	2.7	2.9	4.2	4.3	5.5	4.5	3.6	2.3	2.3	2.5	...	3.9
2.3	1.4	1.7	3.7	3.0	3.1	2.1	1.9	2.3	2.5	2.2	1.9	1.6	1.3	2.1	1.7	1.2	1.7	2.3	1.7	...	...	...	2.5
...	5.4	6.9	4.3	4.3	5.8	4.8	3.9	4.7	4.4	...	...	4.1	4.0	4.1	4.2	4.3	4.6	4.6	...	5.4	...	...	4.6
...	...	1.2	1.7	1.7	1.3	1.5	1.5	1.9	2.0	2.2	1.8	2.0	2.3	2.7	2.8	2.4	1.9	2.7	3.2	...	...	...	2.0

—Number of Deaths Per 100 Cases of Scarlet Fever

1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910	1911	1912	1913	Aver. %
16.4	13.9	9.6	11.3	12.3	8.5	6.8	7.8	7.2	7.2	5.8	8.2	6.2	6.1	5.7	4.6	4.5	5.5	5.8	4.8	4.9	4.8	...	12.2
18.0	13.4	9.9	8.9	6.2	6.1	6.4	7.4	7.6	6.9	9.5	7.8	8.4	7.0	6.3	9.3	5.9	5.9	7.6	5.9	4.8	5.2	...	11.0
4.8	8.9	9.6	8.6	7.1	10.0	7.0	3.8	5.4	10.6	15.0	7.8	4.4	4.0	3.9	2.9	2.1	3.9	3.9	2.8	4.8	2.8	...	7.18
4.2	7.8	11.2	7.4	6.5	5.6	3.4	1.2	3.9	2.6	2.7	3.5	4.3	3.5	4.0	12.0	12.9	4.9	1.6	2.8	4.5	4.0	2.4	7.1
11.5	14.5	7.5	4.4	4.7	2.4	3.3	4.3	3.6	5.8	5.0	5.1	7.9	5.4	4.2	2.4	3.1	3.9	8.1	6.7	7.5	...	...	6.0
...	...	...	...	...	...	...	...	...	...	...	...	...	...	4.9	1.4	4.6	10.2	8.7	15.6	6.7	6.1	10.7	8.7
...	...	...	...	...	...	...	...	...	5.7	5.9	4.5	4.5	5.4	2.9	3.8	5.3	6.8	5.1	7.0	9.3	3.9	...	5.3
...	5.9	4.6	5.0	4.0	2.8	1.7	2.2	1.6	1.8	2.4	2.4	1.3	2.4	3.9	3.5	1.2	2.7	2.8	1.1	1.5	1.5	2.5	2.5
9.6	15.8	7.1	7.0	2.9	3.6	14.6	8.7	8.3	2.5	3.7	10.0	10.4	3.9	2.9	1.6	2.4	2.6	3.4	2.6	2.9	2.4	...	5.4
8.3	12.5	7.0	6.7	5.2	1.7	2.2	3.0	2.2	3.0	3.1	2.5	4.6	3.2	2.6	2.6	1.0	1.9	2.8	1.2	...	1.7	...	9.0
...	...	...	...	...	...	...	7.7	6.8	7.0	7.0	8.1	6.7	6.2	5.9	6.3	5.0	5.5	6.3	5.0	4.6	5.0	...	6.6
...	...	...	...	...	5.1	3.6	3.5	4.1	4.5	3.7	3.8	3.8	2.3	1.1	2.0	2.6	2.4	2.0	2.3	...	...	...	3.0
...	...	...	5.2	4.2	3.7	3.0	3.4	2.2	2.6	3.2	3.1	2.9	2.7	2.8	2.6	2.5	2.5	2.2	2.0	1.6	1.4	...	3.0
6.3	7.3	5.7	3.7	3.9	3.5	3.6	2.7	2.6	3.2	2.4	2.4	3.3	2.4	2.7	2.0	2.1	2.2	2.6	2.0	...	1.7	...	7.9
...	4.5	4.4	4.7	4.1	4.0	4.0	3.7	3.2	3.4	...	...	3.4	3.1	3.3	2.9	2.5	2.6	2.6	...	1.8	...	...	3.3
...	...	15.6	16.7	16.4	13.9	13.2	12.1	12.9	12.2	11.5	...	35.4	39.0	...	...	27.7	...	28.1	28.2	...	...	...	22.3
...	...	...	...	...	...	8.1	9.5	7.0	15.6	6.5	8.8	8.9	8.8	9.0	14.1	12.8	14.9	22.0	19.7	15.0	12.1	...	16.3

tants had scarlet fever, of whom one person in twenty died (Tables 1 and 2).

Susceptibility of Communities.—Comparison of the incidence of the disease in one locality with that in another is expressed in terms of the number of cases per 1,000 inhabitants, or the morbidity rate. Thus, in the thirty-nine years 1874-1912, there were reported in former New York 229,071 cases of scarlet fever (Fig. 1). From the sum of the annual populations of New York for this period, its mean morbidity rate for scarlet fever was found to be 3.2 per 1,000, which means that during these thirty-nine years, an annual average of 3.2 persons per 1,000 inhabitants had this disease.

Without enumerating the periods, which may be seen by reference to Tables 1, 2 and 3, and Figures 1 to 12, the mean morbidity rate for England and Wales was found to be 4.6; for London, 3.9; Nuremberg, 3.3; for the eight American cities, 2.8; Norway, 2.5;

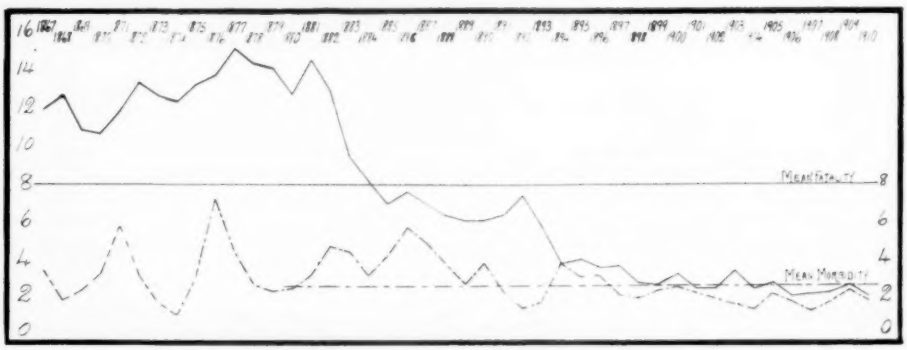

Fig. 11.—Morbidity and case fatality in Norway for forty-four years, from 1867 to 1910, there being 233,587 cases with 18,556 deaths, a case fatality of 7.9 per cent. and a morbidity rate of 2.5 per 1,000 population.

and Paris, 1.8 per 1,000. England had more scarlet fever than any of the other places studied. London has had more than twice as many cases per 1,000 inhabitants as Paris, while Greater New York has occupied a position between the two, with a mean morbidity rate since 1898 of 3.1 per 1,000. The mean morbidity rates of four American cities, over periods of from thirty to forty years were almost identical, being 3.2 for New York, Brooklyn and Providence, and 2.9 for Boston. St. Louis and Philadelphia had identical morbidity rates of 1.9; Washington, 1.5; and Montreal, 2.1 per 1,000. A marked difference in the incidence of scarlet fever in different localities is therefore present. In large cities the disease may be abundant in some parts and slight or absent in others; in London

this is continuously so. In only four of forty years was the incidence of scarlet fever in New York and Brooklyn the same, at times it differed widely, and yet their mean morbidity rates for the entire forty years were identical. (Further illustrations may be seen in Table 3.)

Fatality in Different Localities.—In comparing mortalities of different places it is done in terms of percentage, or deaths per 100 cases (Table 4 and Figs. 1 to 12). It is necessary to compare simultaneous years or periods of years. The mean case fatality of Greater New York since 1898 is 6 per cent., while London and Paris during practically the same period have had only half the case fatality, namely, 3 per cent.; Washington, 2.5 per cent.; Philadelphia, 5.3 per cent. Since 1892 the mean case fatality of England and Wales is 3.3 per cent., and of the Russian Empire, 22.3 per cent. For the past forty years that of former New York is 12.2 per cent., Brooklyn, 11 per cent.; Boston, 7.2 per cent.; and Christiania, 9 per cent.; Norway as a whole, 7.9 per cent.

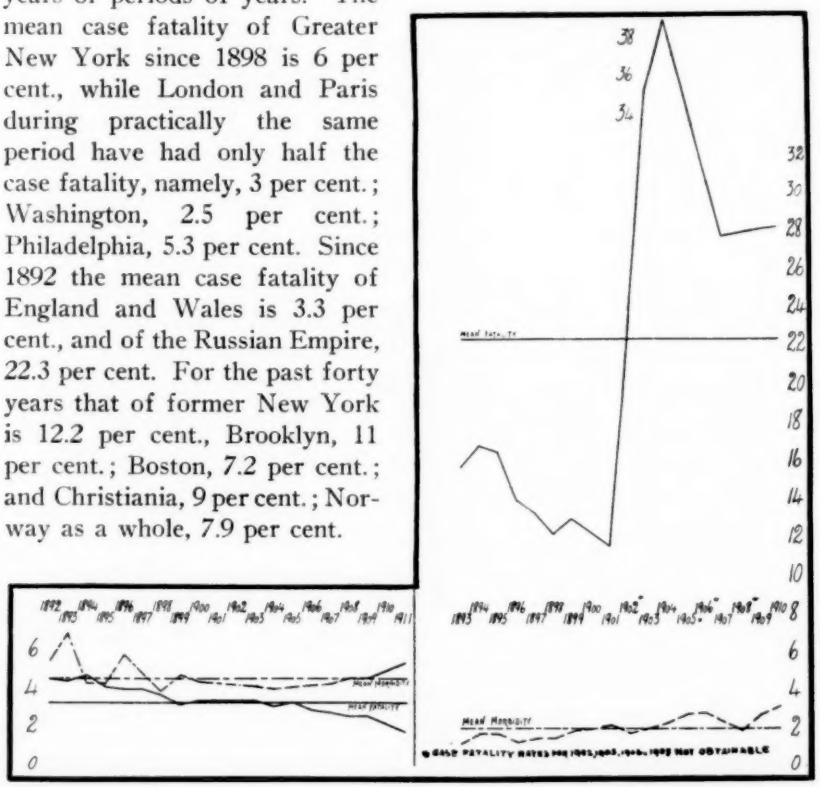

Fig. 12.—Morbidity and case fatality: at the left, in England and Wales, for twenty years, from 1892 to 1911, there being 1,231,018 cases with 41,192 deaths, a case mortality of 3.3 per cent. and a morbidity rate of 4.6 per 1,000 population; at the right, in the Russian Empire, for fourteen years, from 1893 to 1910, there being 3,793,453 cases with 845,641 deaths, a case fatality of 22.3 per cent. and a morbidity rate of 2 per 1,000 population.

Not only is scarlet fever, therefore, more abundant in some places than others, but its fatality in some places is much greater than in others (Table 4). The disease therefore does possess a genius of locality (genius loci).

Periodicity of Occurrence of Scarlet Fever Epidemics.—In all of the places studied scarlet fever is endemic, cases of the disease being

TABLE 5.—Case Fatality by Months and Seasons; the Percentage of the—

Place	Time	No. of Years	Cases, Deaths, % Fatality	January		February		March		April		May	
				Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	
Providence	1885 to 1913	29	15,597 1,084 7%	C 1,924 D 129 6.7%	12.3 11.9	1,520 123 8.1%	9.7 11.3	1,646 116 7%	10.6 10.7	1,656 118 7.1%	10.6 10.9	1,310 96 7.3%	8.4 8.9
St. Louis (14,052)	1900 to 1911	11	14,099 853 6.1%	C 1,589 D 76 4.8%	11.3 8.9	1,389 91 6.6%	9.9 10.7	1,724 87 5.0%	12.3 10.2	1,667 94 5.6%	11.9 11.0	1,652 115 7.0%	11.8 13.4
Washington	1892 to 1913	22	9,476 238 2.5%	C 1,397 D 28 3%	14.7 11.8	1,023 31 3%	10.8 13.0	1,029 33 3.2%	10.9 13.9	779 26 3.3%	8.2 10.9	763 27 3.5%	8.1 11.3
Montreal	1905 to 1913	9	7,820 684 8.7%	C 728 D 60 8.2%	9.3 8.8	711 66 9.3%	9.1 9.6	920 94 10.2%	11.8 13.7	830 85 10.2%	10.6 12.4	791 84 10.6%	10.1 12.3
Nuremberg	1890 to 1912	23	18,654 993 5.3%	C 1,659 D 83 5.0%	8.9 8.4	1,538 91 5.9%	8.2 9.2	1,595 90 5.6%	8.6 9.1	1,469 76 5.2%	7.9 7.7	1,463 69 4.7%	7.8 7.7
Japan	1897 to 1912	16	8,882 1,452 16.3%	C 695 D 113 16.3%	7.8 7.8	773 135 17.5%	8.7 9.3	1,039 152 14.6%	11.7 10.5	1,042 152 14.6%	11.7 10.5	934 128 13.7%	10.5 8.8
Total cases (74,481) Total deaths Case fatalities, %	....	....	74,528 5,304 7.1%	C 7,992 D 489 6.1%	9.2	6,954 537 7.7%	10.1	7,953 572 7.2%	10.8	7,443 551 7.4%	10.4	6,913 519 7.5%	9.8
Philadelphia	1908 to 1912	5	11,965 741 6.2%	C 1,092	9.1	1,043	8.7	1,296	10.8	1,332	11.1	1,339	11.2
Paris (75,456)	1896 to 1910	15	72,189 2,142 3%	C 5,395	7.1	5,847	7.7	7,281	9.6	7,939	10.5	9,750	12.9
Norway (232,797)	1867 to 1910	43	233,587 18,556 7.9%	27,298	11.7	22,221	9.5	20,881	9.0	17,453	7.5	17,670	7.6
Grand total cases (394,699) Grand total deaths	....	....	392,269 26,743 6.8%	C 41,777	10.6	36,065	9.1	37,411	9.1	34,167	8.7	35,672	9.1
England and Wales	1892 to 1900	9	.....	January-February-March Cases 112,627 Deaths 5,225 Fatality, % 4.6						April-May- Cases 118,467			June Dea 5,0

—Cases Occurring in Each Month; the Percentage of Deaths in Each Month

May	June		July		August		September		October		November		December	
Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total	Cases, Deaths, % Fatality	Mo.'s % of Year's Total
8.4	996	6.4	646	4.1	661	4.2	846	5.4	1,318	8.5	1,442	9.2	1,632	10.5
8.9	63 6.3%	5.8	49 7.6%	4.5	54 8.2%	5.0	57 6.7%	5.3	89 6.8%	8.2	87 6.0%	8.2	103 6.3%	9.5
11.8	1,107	7.9	524	3.7	409	2.9	577	4.1	808	5.8	1,189	8.5	1,417	10.1
13.4	91 8.2%	10.7	44 8.4%	5.2	41 10.0%	4.8	32 5.5%	3.8	46 5.7%	5.4	57 4.8%	6.7	79 5.6%	9.3
8.1	530	5.6	333	3.5	422	4.5	418	4.4	748	7.9	908	9.5	1,131	11.9
11.3	16 3%	6.7	8 2.4%	3.4	11 2.6%	4.6	4 1%	1.7	17 2.3%	7.1	15 1.7%	6.3	22 1.9%	9.2
10.1	618	7.9	400	5.1	372	4.8	451	5.8	564	7.2	626	8.0	809	10.3
12.3	43 7%	6.3	30 7.5%	4.4	35 9.4%	5.1	28 6.2%	4.1	46 8.2%	6.7	55 8.8%	8.0	58 7.2%	8.5
7.8	1,463	7.8	1,380	7.4	1,209	6.5	1.413	7.6	1,931	10.4	1,870	10.0	1,664	8.9
7.7	88 6.0%	8.9	81 5.9%	8.2	86 7.1%	8.7	72 5.1%	7.3	78 4.0%	7.9	94 5.0%	9.5	85 5.1%	8.6
10.5	825	9.3	677	7.6	378	4.3	318	3.6	561	9.3	771	8.7	869	9.8
8.8	151 18.3%	10.4	131 19.4%	9.0	70 18.5%	4.8	61 19.2%	4.2	84 15.0%	5.8	114 14.8%	7.9	161 18.5%	11.1
9.8	5,539 452 8.2%	8.5	3,960 343 8.7%	6.5	3,451 297 8.6%	5.6	4,023 254 6.3%	4.8	5,930 360 6.1%	6.8	6,801 422 6.2%	7.9	7,522 508 6.8%	9.6
11.2	1,029	8.6	514	4.3	429	3.6	497	4.2	870	7.3	1,105	9.2	1,419	11.9
12.9	9,777	13.0	8,698	11.5	4,540	6.0	2,917	3.9	3,830	5.1	4,395	5.8	5,087	6.7
7.6	17,391	7.5	14,711	6.3	13,772	5.9	14,443	6.2	19,426	8.3	23,831	10.2	23,700	10.2
9.0	33,736	8.5	27,883	7.1	22,192	5.6	21,880	5.5	30,056	7.6	36,132	9.2	37,728	6.0

June			July–August–September			October–November–December		
Deaths	Fatality, %		Cases	Deaths	Fatality, %	Cases	Deaths	Fatality, %
5,090	4.3		149,730	5,440	3.6	176,793	6,754	3.7

practically always present; the fluctuations in the amount, as shown by the annual morbidity rates, follow no rule as regards periodicity, in contrast to what one sees stated by some authors (Figs. 1 to 12). The prevalence of the disease may be increased for a single year, the previous and succeeding years being below the average, but it is more common to see two, three, and less often four or even five years in succession, in which the amount of scarlet fever is increased. In other words, an epidemic either subsides slowly during two or three or more years, or may attain a greater height in its second than in its first year. It goes slowly or comes slowly, as compared to measles, for instance, in which an epidemic attains its height very quickly and subsides equally so. There may be but a single year between epidemics of scarlet fever, or there may be two, three, four, five or more years between them, with low morbidity rates during the interim. A standard for judging the prevalence of scarlet fever in a community at any given time is found only in the mean morbidity rate of the community in question.

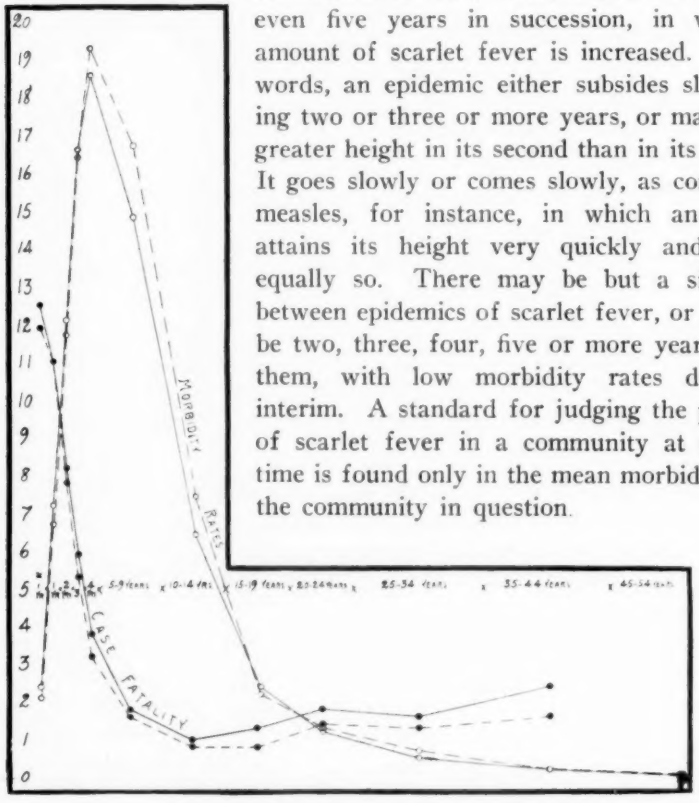

Fig. 13.—Graphic representation of the last two double columns in Table 7. Figures 14, 15, 16, 17 and 18 are made in the same way as 13, except where figures for the sexes were not to be had. Morbidity and case fatality, as influenced by age and sex, in London, for nineteen years, from 1894 to 1912, there being 159,077 cases among males, with 5,206 deaths, a case fatality of 3.3 per cent. and a morbidity rate of 3.96 per 1,000 population; 176,349 cases among females, with 4,817 deaths, a case fatality of 2.7 per cent. and a morbidity rate of 3.92 per 1,000 population. The solid lines represent the data for males; the broken lines for females.

Decrease of Incidence.—There has been no striking reduction in the annual morbidity rates anywhere during the periods studied (Table 3 and Figs. 1 to 12). They fluctuate from year to year within essentially the same limits now as years ago. The smaller the place, the greater are the annual fluctuations in morbidity rates.

This is seen particularly in Christiania (Fig. 10), the smallest place studied. On the other hand, where the annual rates for the whole of England and Wales (Fig. 12) are compared, the localities included are so numerous and different that there is a consolidation of local differences, so that the rates for the whole country fluctuate from year to year within comparatively narrow limits. Norway (Fig. 11) shows a decided tendency to a decline in the prevalence of scarlet fever and the same is true of Philadelphia (Fig. 6). The Russian Empire (Fig. 12) and Montreal (Fig. 8) show tendencies in the opposite direction, namely toward an increase in morbidity rates.

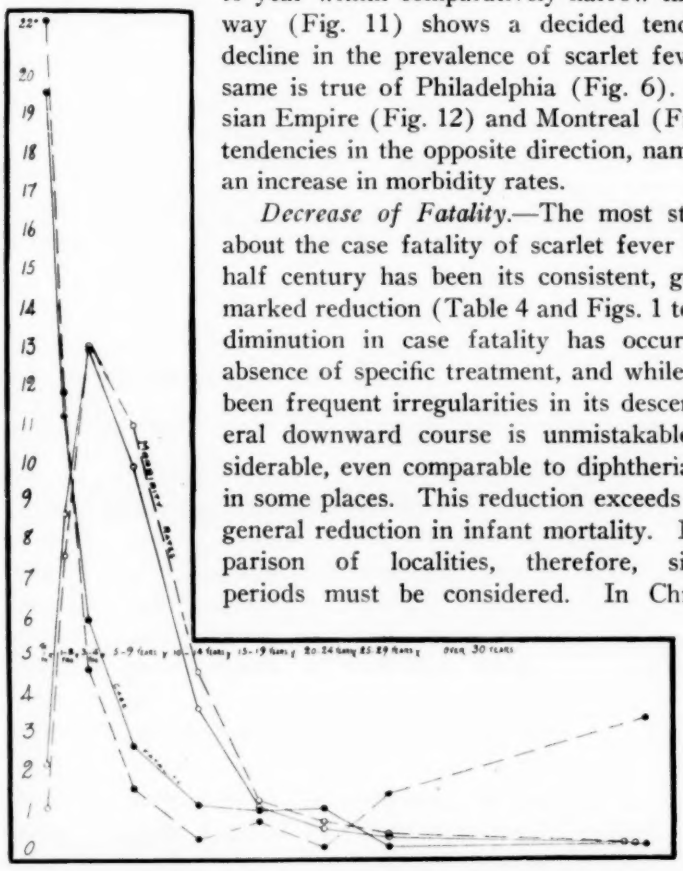

Fig. 14.—Morbidity and case fatality, as influenced by age and sex, in Christiania, for twenty-one years, from 1890 to 1910, there being 5,656 cases among males, with 271 deaths, a case fatality of 4.8 per cent. and a morbidity rate of 2.83 per 1,000 population; 6,122 cases among females, with 210 deaths, a case fatality of 3.43 per cent. and a morbidity rate of 2.51 per 1,000 population. The solid lines represent the data for males; the broken lines for females.

Decrease of Fatality.—The most striking fact about the case fatality of scarlet fever in the past half century has been its consistent, general, and marked reduction (Table 4 and Figs. 1 to 12). This diminution in case fatality has occurred in the absence of specific treatment, and while there have been frequent irregularities in its descent, the general downward course is unmistakable and considerable, even comparable to diphtheria in its fall in some places. This reduction exceeds that of the general reduction in infant mortality. In the comparison of localities, therefore, simultaneous periods must be considered. In Christiania in the past five years the case fatality ranged from 1 to 2.8 per cent.; between forty and fifty years ago it varied from 8 to 30 per cent. In Norway, as a whole, it has lately been in the neighborhood of 2 per cent.; forty to fifty years ago it was from 12 to 15 per cent. In former New York and Brooklyn it has lately been in the vicinity of

TABLE 6.—Comparison of Sexes in Population—

Place and Time	Number of Years	Total of Annual Populations	Populations	
			Males	Females
Nuremberg (1890 to 1912)	21	5,282,848	2,606,486	2,676,362
London (1894 to 1912)	19	85,186,789	40,171,943	45,014,846
Norway (1880 to 1910)	30	65,302,907	31,517,229	33,785,678
Totals	.....	155,772,544	74,295,658	81,476,886

* This table shows morbidity rates by sex to be almost identical; and the sexes in practically the same proportion among the population and the cases. Case fatality is higher among males.
† The cases among males were 47.82 per cent. of the whole number of cases; those among females, 52.18 per cent.

TABLE 7.—Distribution of Morbidity and—
(London, 1894-1912—

Age, Years	Population		Population in Percentage		Cases of Scarlet Fever	
	Males	Females	Males	Females	Males	Females
Under 1	992,009	988,546	50.08	49.92	2,376	2,035
1	899,960	896,932	50.08	49.92	6,509	6,045
2	947,475	941,368	50.16	49.84	11,467	11,003
3	925,265	936,942	49.68	50.32	15,326	15,354
4	903,504	902,521	50.02	49.98	16,794	17,373
5 to 9	4,268,466	4,301,869	49.80	50.20	63,150	71,939
10 to 14	3,918,305	3,989,812	49.54	50.46	25,085	29,665
15 to 19	3,782,466	4,170,392	47.56	52.44	9,015	9,119
20 to 24	3,730,462	4,579,650	44.89	55.11	4,490	6,156
25 to 34	6,815,812	7,989,570	46.03	53.97	3,638	5,846
35 to 44	5,322,498	5,977,617	47.10	52.90	910	1,359
45 to 54	3,826,080	4,304,297	47.05	52.95	237	322
55 and over	3,839,623	5,035,330	43.26	56.74	80	133
Totals	40,171,943	45,014,846	47.20	52.80	159,077	176,349
Grand total	85,186,789		.....	.....	335,426	

* This table (in part represented graphically in Figure 13) shows in the last two double columns case fatality and morbidity rates with distinction of sex and age. For example, at the age of 4 years, the case fatality among boys was 3.8 per cent. and 3.2 per cent among girls. Out of each 1,000 living boys

—AND AMONG SCARLET FEVER CASES AND DEATHS*

Population, per Cent.		Morbidity Rate per 1,000		Scarlet Fever Cases†		Deaths from Scarlet Fever‡		Case Fatality, per Cent.	
Male	Female	Male	Female	Males	Females	Males	Females	Males	Females
49.3	50.7	3.19	3.55	8,324	9,497	502	475	6.03	5.0
47.2	52.8	3.96	3.92	159,077	176,349	5,206	4,817	3.27	2.73
48.3	51.7	2.49	2.43	78,263	82,203	5,344	4,545	6.83	5.53
47.7	52.3	3.31	3.29	245,664	268,049	11,052	9,837	4.50	3.67

‡ The deaths among males were 53 per cent. of the whole number of deaths; those among females, 47 per cent.

—CASE FATALITY ACCORDING TO SEX AND AGE —NINETEEN YEARS)*

Cases in Percentage		Deaths from Scarlet Fever		Deaths in Percentage		Percentage of Case Fatality		Morbidity Rates per 1,000	
Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
53.87	46.13	297	242	55.10	44.90	12.5	11.9	2.4	2.1
51.85	48.15	717	662	51.99	48.01	11.0	11.0	7.2	6.7
51.03	48.97	944	856	52.44	47.56	8.2	7.8	12.1	11.7
49.95	50.05	907	815	52.67	47.33	5.9	5.3	16.6	16.4
49.15	50.85	682	556	53.20	46.80	3.8	3.2	18.6	19.3
46.75	53.25	1,162	1,172	49.79	50.21	1.8	1.6	14.8	16.7
45.82	54.18	256	241	51.51	48.49	1.0	0.8	6.4	7.4
49.71	50.29	114	75	60.32	39.68	1.3	0.8	2.4	2.2
42.18	57.82	81	86	48.50	51.50	1.8	1.4	1.2	1.3
38.36	61.64	50	77	43.38	56.62	1.6	1.3	0.5	0.7
40.11	59.89	22	21	51.16	48.84	2.4	1.6	0.2	0.2
42.40	57.60	12	9	57.14	42.86	5.1	2.8	0.06	0.07
37.56	62.44	3	5	37.50	62.50	3.8	3.8	0.02	0.02
.....	.....	5,206	4,817	.....	.....	3.3	2.7	3.96	3.92
.....	.....	10,023							

at the age of 4 years 18.6 had scarlet fever. Similarly, 19.3 out of each 1,000 living girls of 4 years had scarlet fever. Absolute figures and ratios of the sexes in the population, the reported cases and deaths for scarlet fever, at various ages, are presented.

5 per cent., compared to from 20 to 35 per cent. forty years ago. In Nuremberg the recent fatality is in the neighborhood of 3 per cent., while twenty years ago 7 to 15 per cent. was more common.

In contrast to the rule of diminishing case fatality, attention must be called to the fact that in the Russian Empire (Fig. 12) the later case fatality has been in the neighborhood of 30 per cent., while twenty years ago it was only half this amount. Japan (Fig. 7) likewise has a case fatality which has a decided tendency toward increase. As yet the amount of scarlet fever in Japan according to its health reports is exceedingly small.

In Australia and New Zealand there have been very low morbidity rates and case fatality (1.5 per cent.).

Explanation of Lowered Fatality.—Heubner says:

> Sydenham in the year 1664 looked upon scarlet fever as possessing no great importance, about as we today regard German measles, and fifteen years later it appeared in the practice of this great clinician in London with a formidability which was scarcely inferior to plague. A century and a half later a physician of equal rank, Bretonneau, stated that a scarlet fever patient died only when he was wrongly treated, but was obliged a few years later to confess how greatly he had erred when he found himself in the midst of an epidemic with a shocking mortality.

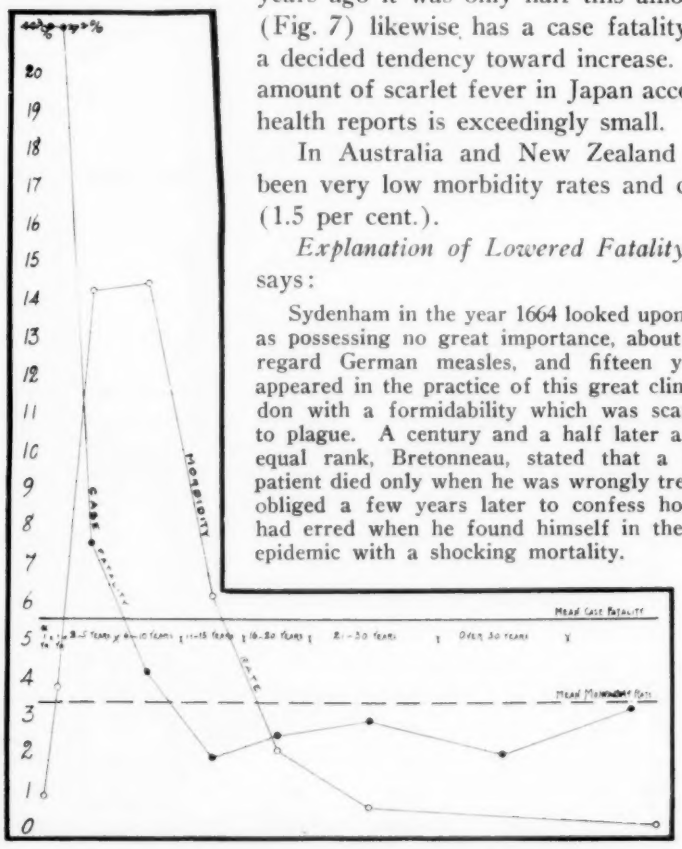

Fig. 15.—Morbidity and case fatality as influenced by age, in Nuremberg, for twenty-three years, from 1890 to 1912, there being 17,835 cases with 977 deaths, a case fatality of 5.5 per cent. and a morbidity rate of 3.32 per 1,000 population.

In the reports of the Local Government Board, London, for 1909-1910, the medical officer said: "There can be no doubt in the minds of those who knew scarlet fever as it existed thirty or forty years ago that it is at present a much milder disease."

There is certainly evidence to favor the opinion that the disease is milder today than formerly.

The removal of scarlet fever patients to contagious hospitals has improved the care of many patients and may be a contributing factor to lowered fatality. Over 90 per cent. of the patients in London are treated in contagious hospitals, whereas in 1890 there were but 42.8 per cent. thus treated. As patients in hospitals are usually given diphtheria antitoxin, it is quite probable that this is another important factor, because combined scarlet fever and diphtheria have had a high fatality.

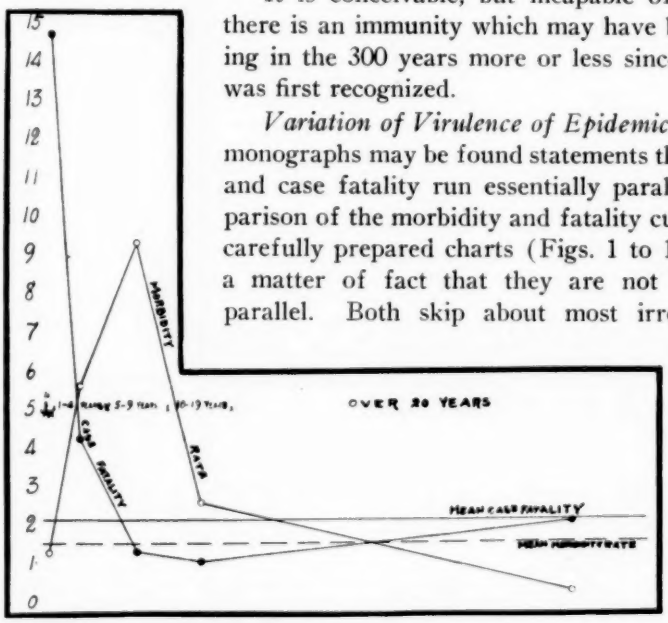

Fig. 16.—Morbidity and case fatality, as influenced by age, in Washington, D. C., for six years, from 1908 to 1913, there being 3,320 cases with 68 deaths, a case fatality of 2.1 per cent. and a morbidity rate of 1.5 per 1,000 population.

It is conceivable, but incapable of proof, that there is an immunity which may have been increasing in the 300 years more or less since the disease was first recognized.

Variation of Virulence of Epidemics.—In recent monographs may be found statements that morbidity and case fatality run essentially parallel. A comparison of the morbidity and fatality curves on very carefully prepared charts (Figs. 1 to 12) shows as a matter of fact that they are not in the least parallel. Both skip about most irregularly. A large epidemic may have a low case fatality, or it may have a high case fatality which diminishes as the epidemic increases. On the other hand, a small incidence of scarlet fever may be attended with a high case fatality, while at another time in the same place a like morbidity may be attended by a low case fatality. Grouping the figures from various localities obscures local differences in morbidity and fatality and conceals striking variations in them.

Influence of Season.—The height of an epidemic of scarlet fever may occur at any season of the year (Table 5). January and December usually have the maximum number of cases, and August and September the smallest number. In Paris the maximum number is quite

TABLE 8.—Scarlet Fever as Influenced by School (London)*

Year	Cases in Last Four Weeks of School			Cases in Vacation Four Weeks (August)						Cases in First Four Weeks of School					
	0 to 3 Years	3 to 13 Years	Over 13 Years	0 to 3 Years	Change, %	3 to 13 Years	Change, %	Over 13 Years	Change, %	0 to 3 Years	Change, %	3 to 13 Years	Change, %	Over 13 Years	Change, %
1911	110	650	98	80	—27.3	460	—29.2	111	+13.3	91	+13.7	836	+81.7	154	+38.7
1910	94	609	114	87	— 7.4	499	—18.1	92	—19.3	86	— 1.1	624	+25.1	113	+22.8
1909	187	1,100	215	148	—20.9	812	—26.2	169	—21.4	174	+17.6	1,238	+52.5	222	+31.4
1908	161	1,206	230	169	+ 5.0	1,075	—10.9	214	— 7.0	234	+38.5	1,537	+43.0	323	+50.9
1907	270	1,540	316	259	— 4.1	1,429	— 7.2	304	— 3.8	283	+ 9.3	2,065	+44.5	389	+28
1906	184	1,330	233	195	+ 6	947	—28.8	208	—10.7	182	— 6.7	1,471	+55.3	309	+48.6
1905	186	1,093	186	208	+11.8	1,160	+ 6.1	189	+ 1.6	219	+ 5.3	1,647	+42	263	+39.2
1904	126	839	139	98	—22.2	638	—24	144	+ 3.6	145	+48	967	+51.6	164	+13.9
1903	123	810	157	163	+32.5	612	—24.4	127	—19.1	124	—23.9	789	+28.9	174	+37
1902	186	1,143	257	203	+ 9.1	889	—22.7	270	+ 5.1	180	—11.3	1,086	+22.9	234	—13.3
1901	184	1,141	352	169	— 8.2	890	—22	281	—20.2	193	+14.2	1,391	+56.3	382	+35.9
1900	108	607	202	90	—16.7	512	—15.7	182	— 9.9	108	+20	895	+68.9	263	+44.5
1899	175	1,051	246	141	—19.4	793	—24.5	238	— 3.3	167	+18.4	1,220	+53.8	301	+26.5
1898	176	997	197	137	—22.2	680	—31.8	163	—17.3	136	— 0.7	907	+33.4	194	+19
1897	260	1,416	335	233	—10.4	1,240	—12.4	318	— 5.1	249	+ 6.9	1,803	+45.4	327	+ 2.8
1896	275	1,681	420	348	+26.5	1,632	— 2.9	496	+18.1	350	+ 0.6	1,960	+21.3	369	—25.6
1895	234	1,390	312	252	+ 7.7	1,084	—22	254	—18.6	229	— 9.1	1,518	+40	334	+31.5
1894	204	1,026	220	189	— 7.4	808	—21.2	181	—17.7	176	— 6.9	1,079	+33.5	175	— 3.3
Totals	3,243	19,629	4,229	3,169	— 2.28	16,160	—17.67	3,941	— 6.81	3,326	+ 4.95	23,053	+42.65	4,690	+19.0

* This table shows the cases of scarlet fever reported in London, 1894 to 1911, for the last four weeks of school, during the four weeks vacation in August, and the first four weeks after schools opened. The greatest change took place in children of school age, 3 to 13 years. The percentages of fall and increase in case reports are shown.

constantly in the early summer. Case fatality is highest in the summer months, lowest in the fall.

Susceptibility of Sexes.—Quite a difference is to be found in the absolute numbers of cases in the two sexes, the higher number representing the females. The reason for this is made clear if we consider the composition of the general population, where it is found that the total number of females is considerably greater than the total number of males. The writer has calculated the number of cases of scarlet fever per 1,000 males in the population, and the same for females and found that the morbidity rates thus obtained for the two sexes are almost identical. The number of cases of scarlet fever among males bears almost the same ratio to the number of cases among females as the number of males bears to the number of females in the entire population (Table 6). The slight difference which exists, however, shows a slightly increased susceptibility among males. Roughly, however, we may say that the sexes as a whole show about equal susceptibility. During the first four years of life boys are more susceptible to the disease, while between 5 and 15 years girls are distinctly more susceptible (Table 7 and Figs. 13, 14, 21, 22 and 23). Otherwise sex has little or no influence on susceptibility.

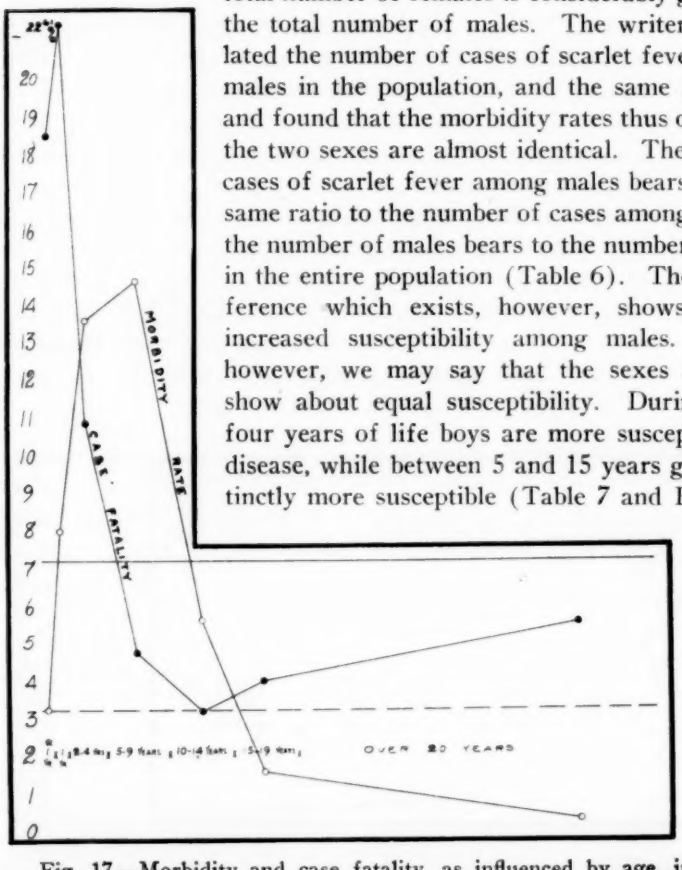

Fig. 17.—Morbidity and case fatality, as influenced by age, in Providence, for twenty-seven years, from 1887 to 1913, there being 14,278 cases with 1,017 deaths, a case fatality of 7.12 per cent. and a morbidity rate of 3.2 per 1,000 population.

Nichols[4] has shown by means of a stupendous compilation of birth statistics that about 1,056 boys are born to each 1,000 girls. The pre-

3. Nichols, J. B.: The Numerical Proportions of the Sexes at Birth, Am. Anthropol. Assn., Memoirs, Lancaster, Pa., 1907, i, Part 4.

ponderance of boys over girls in the population keeps up until about the age of 20 years, and thereafter women predominate. This only accentuates the peculiar sex preference of scarlet fever just mentioned, namely, greater the first 4 years among boys; greater among girls from 5 to 15 years.

Sex as Influencing Fatality.—The number of deaths from scarlet fever is both absolutely and relatively greater in boys than in girls, the deaths among boys ranging from 50.5 to 53.7 per cent. of the total deaths. Among 513,713 cases, there occurred 20,889 deaths, of which 53 per cent. were among boys and 47 per cent. among girls. The case fatality among boys was 4.5 per cent., as against 3.67 per cent. among girls, and in each of the localities case fatality was higher among boys. For Norway case fatality among boys was 6.83 per cent. against 5.53 per cent. for girls; in London 3.27 per cent. against 2.73 per cent., and in Nuremberg 6.03 per cent. against 5 per cent. It is thus seen that case fatality is 20 per cent. greater among boys than among girls. Furthermore, it is consistently higher for males at

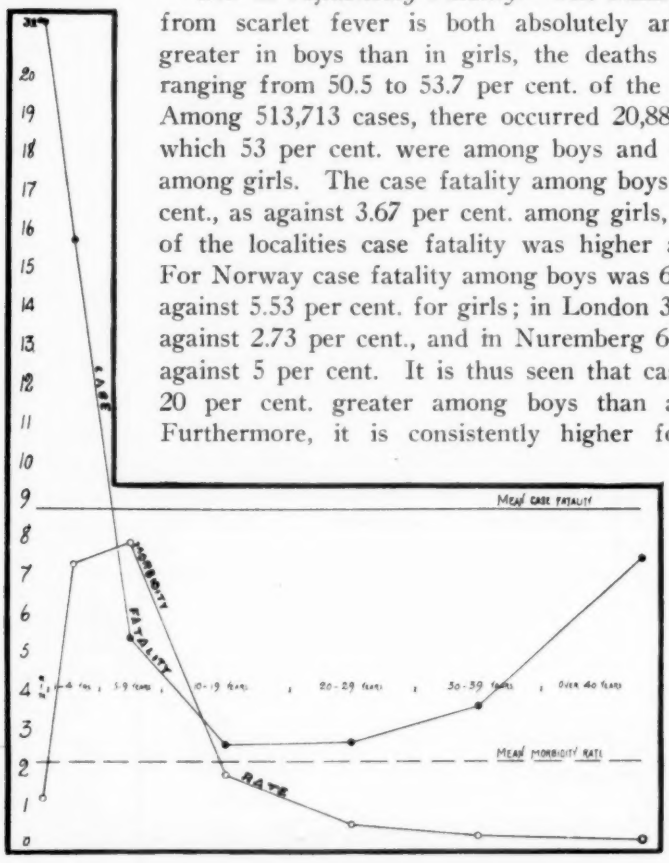

Fig. 18.—Morbidity and case fatality, as influenced by age, in Montreal, for nine years, from 1905 to 1913, there being 7,820 cases with 684 deaths, a case fatality of 8.7 per cent. and a morbidity rate of 2.1 per 1,000 population.

each age period throughout life (case fatality curves, Figs. 13 and 14).

Age of Greatest Susceptibility.—Nearly half of all cases of scarlet fever occur in children at the ages 3, 4, 5, 6 and 7 years, and are quite evenly distributed at about 10 per cent. in each of these years (Fig. 19). Board of Health figures show somewhat over 1 per cent. of cases

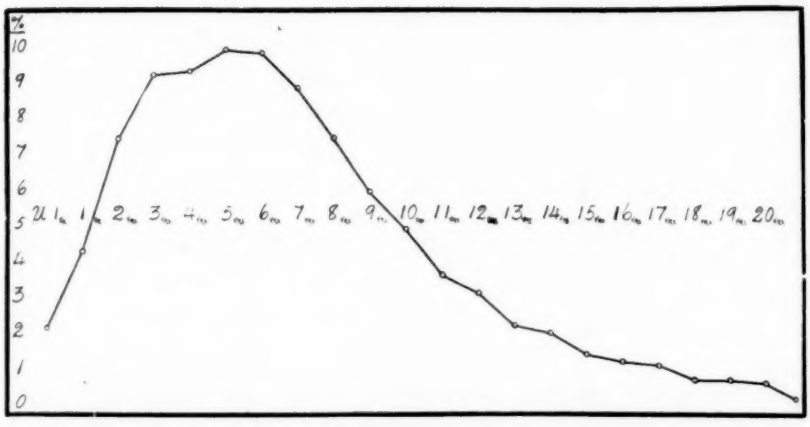

Fig. 19.—Age distribution of scarlet fever in the years up to 20, expressed for each year in percentage of the total, in Providence, for twenty-seven years, from 1887 to 1913, there being 14,278 cases.

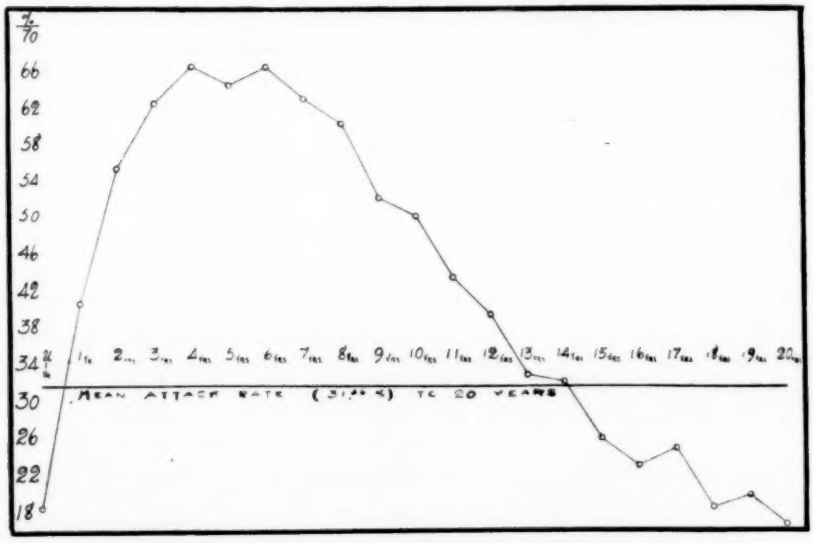

Fig. 20.—Age susceptibility to scarlet fever, in Providence, for twenty-seven years, from 1887 to 1913, based on 45,388 persons, not previously having had the disease, exposed in their own homes; there were 14,278 cases resulting, or an average of 31.5 per cent. for all ages up to 20 years.

occurring in children under 1 year of age,[4] the incidence rising rapidly to age 3, where it remains level for five years, falling by age 15 to about 1 per cent.

At the ages 3, 4, 5, 6 and 7 years, about two children out of three contract scarlet fever if exposed to it in their homes (Fig. 20).

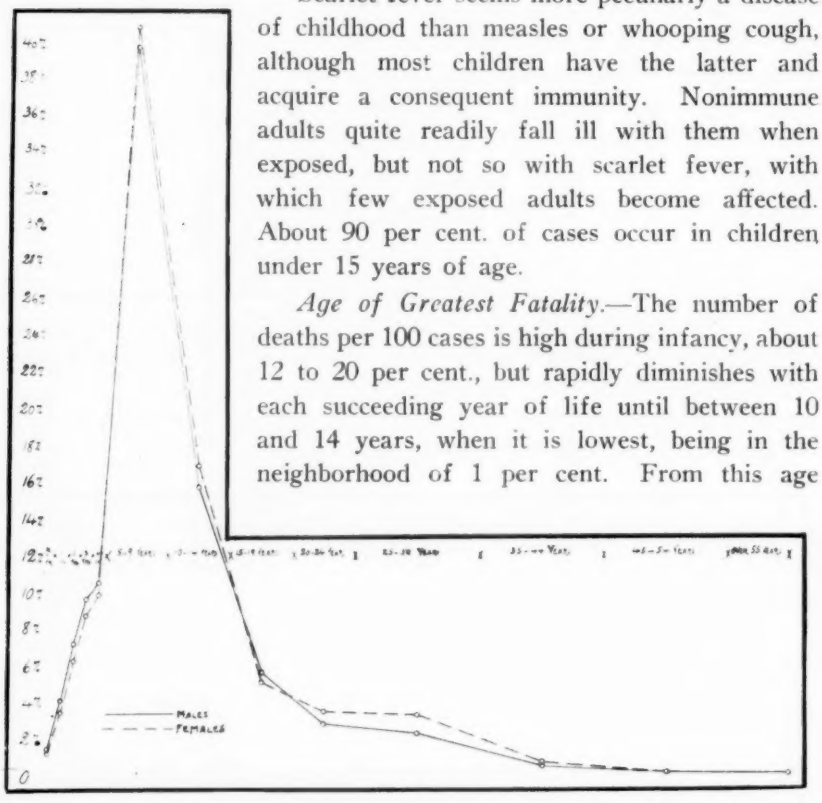

Fig. 21.—Distribution of cases in percentage of the total for each sex at the various ages of life, in London, for nineteen years, from 1894 to 1912, there being a total of 335,426 cases, 159,077 among males, or 47.43 per cent., and 176,349 among females, or 52.57 per cent. of the total.

Scarlet fever seems more peculiarly a disease of childhood than measles or whooping cough, although most children have the latter and acquire a consequent immunity. Nonimmune adults quite readily fall ill with them when exposed, but not so with scarlet fever, with which few exposed adults become affected. About 90 per cent. of cases occur in children under 15 years of age.

Age of Greatest Fatality.—The number of deaths per 100 cases is high during infancy, about 12 to 20 per cent., but rapidly diminishes with each succeeding year of life until between 10 and 14 years, when it is lowest, being in the neighborhood of 1 per cent. From this age on the disease has a slowly increasing death rate (case fatality curves, Figs. 13 to 18).

About 90 per cent. of deaths occur in children under 10 years of age.

4. A proportion of 1 + per cent. for cases of scarlet fever in children under 1 year of age is regarded by clinicians of wide experience as very high, and they properly raise the question of accuracy of diagnosis in young babies reported as having the disease.

CONCLUSIONS

Figures obtained from board of health notifications of cases and deaths for scarlet fever, support the following conclusions:

Periodicity in the appearance of epidemics of scarlet fever cannot be made out.

Morbidity and mortality rates for scarlet fever seem independent of each other.

A decline in morbidity has not generally been made out. (Notification is at present probably more thorough than ever before. While insusceptible of proof, it is probable that this factor has served to keep morbidity rates in most places approximately level.)

Where notification has been of longest duration and most thorough (Norway) a reduction in the incidence of scarlet fever has been observed.

Season itself does not influence morbidity.

The sexes as a whole show equal susceptibility. Under 5 years of age boys are more susceptible, while between 5 and 15 years of age girls are more susceptible than boys.

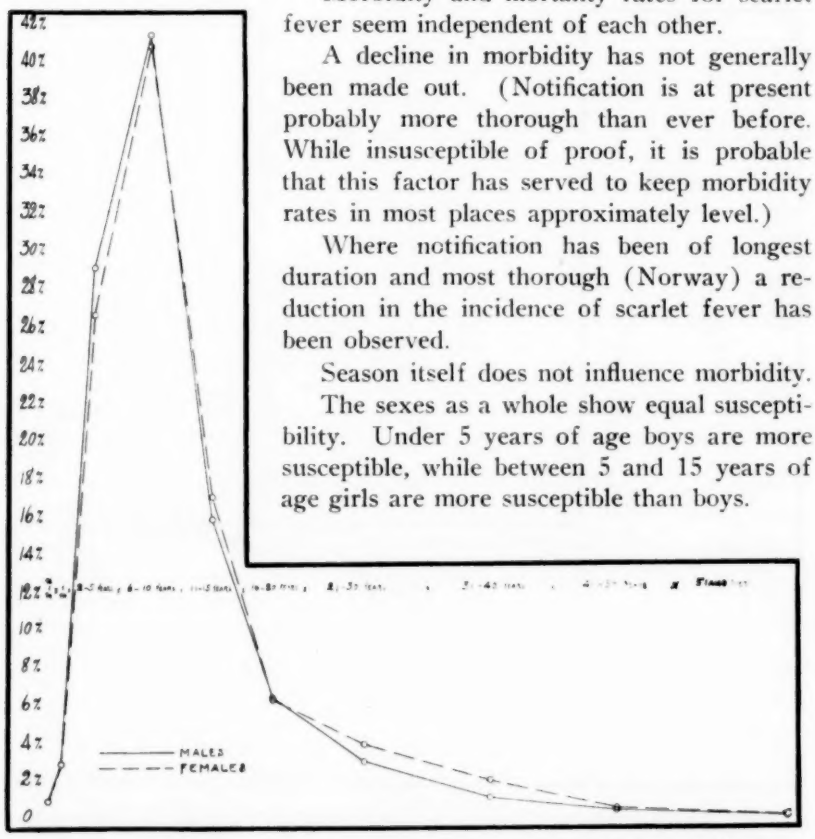

Fig. 22.—Distribution of cases in percentage of the total for each sex at the various ages of life, in Nuremberg, for twenty-one years, from 1890 to 1910, there being a total of 17,821 cases, 8,324 among males, or 46.71 per cent., and 9,497 among females, or 53.29 per cent. of the total.

About half of the cases occur in children between 3 and 8 years, and 90 per cent. in those under 15 years of age.

About two children out of three between 3 and 8 years of age contract scarlet fever if exposed to it in their homes, if they have not previously had it.

Scarlet fever appears to be a milder disease than formerly.

Different epidemics may vary greatly in virulence.

Scarlet fever has been regularly more prevalent in some places than in others.

It has been consistently attended by greater fatality in some places than in others.

At all ages males succumb more readily to it than females.

Case fatality is lowest in those about 10 to 15 years of age. The younger the child, the less is his chance of recovery.

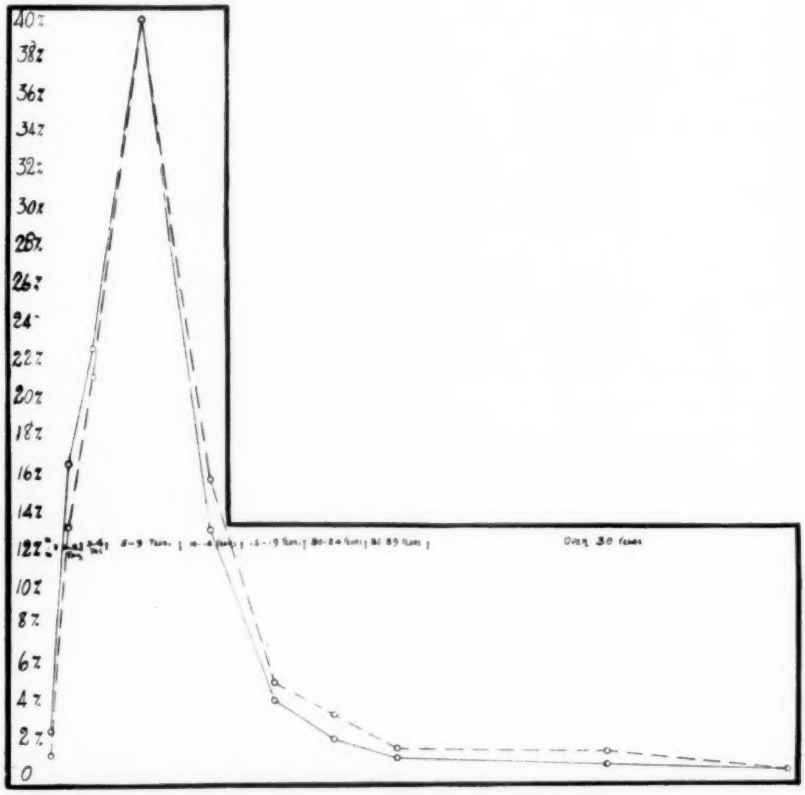

Fig. 23.—Distribution of cases in percentage of the total for each sex at various ages, in Christiania, for twenty-one years, from 1890 to 1910, there being a total of 11,778 cases, 5,656 among males, or 48.02 per cent., and 6,122 among females, or 51.98 per cent. of the total. The solid line indicates the data for males; the broken line, for females.

About 90 per cent. of deaths from scarlet fever occur in those under 10 years of age.

Officials of the Library of the Surgeon-General's Office, Mr. Starkey in particular, have generously rendered much aid in procuring health reports from various parts of the world, from which the figures were obtained. Dr. Frederick S. Crum, assistant statistician of the Prudential Insurance Company, gave valuable assistance in obtaining statistics of populations with distinction of sex and age.

1612 I Street.

CONGENITAL DEXTROCARDIA WITH PATENT DUCTUS OVALE

NECROPSY AT NINE MONTHS *

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In view of the rarity of congenital dextrocardia alone, as shown by the review of the literature recently published by Moffett and Neuhoff,[1] this case is reported. As in almost all cases reported this patient suffered from congenital defect of the heart itself. Its occurrence in a girl and the opportunity for necropsy are interesting features.

CASE REPORT

Jean M., a girl, aged about 1 month, was brought to the Maternity and Children's Hospital for adoption, August 18, 1915.

On physical examination the baby was found to weigh 5 pounds 5 ounces and its length of body to be 18¾ inches, circumference of head 13¼ inches, of chest 11½ inches. The temperature was 99, pulse 144, respiration 40.

The skin of the whole body was cyanotic, more marked over the face and hands. The respiration was rapid, with a sinking in of the suprasternal notch and epigastrium on inspiration, and an active movement of alae nasi. The conjunctivae were congested, but otherwise the eyes, ears, nose and throat were normal.

The respiration was wheezing and difficult, and most râles were perceptible over both lungs in front and at the back, but no other abnormalities of the lungs were present.

The apex of the heart was felt on the right side 6 cm. to the right of the midsternal line at the fourth interspace; the right border at the fifth interspace was 5½ cm., at the fourth interspace 6 cm., at the third interspace 5½ cm. to the right of the midsternal line; the left border was 1 cm. to the left of the midsternal line at the fourth interspace, and the upper border was at the second interspace on the right side. At the first examination a distinct, rough, systolic murmur was heard, loudest at the apex, but more or less distinct over the whole cardiac area. It was not transmitted, and no thrill was felt.

Above the heart in the second interspace an area of dullness extending 3 cm. to the left of the midsternal line was felt. This was taken to be the enlarged thymus.

The liver and spleen seemed to be in normal position. No bony changes and no clubbing of the fingers were present, and no other abnormalities could be detected. A roentgenogram taken at this time (Fig. 1) shows the correctness of the foregoing findings.

Blood examination showed hemoglobin 130 per cent. (Sahli), red cells 6,250,000, white cells 9,200, polymorphonuclears 47.5 per cent., large leukocytes 20 per cent., small leukocytes 32.5 per cent., with no abnormal red cells.

The thymic enlargement and the wheezing, bubbling character of the respiration suggested the possibility of thymic asthma, and so the baby was treated by Roentgen-ray exposures, as outlined in a report of cases of this disorder successfully treated by us,[2] but no benefit followed.

Except for a gain of 4 pounds 14 ounces in the next eight and one-half months no marked changes occurred in her condition. While her color was

* Submitted for publication May 22, 1916.

1. Moffett and Neuhoff: Am. Jour. Dis. Child., 1915, x, 1.
2. Morgan and Dachtler: Surg., Gynec. and Obst., 1914, xix, 781.

at times fairly good, she usually showed slight cyanosis of the face and hands, and when exposed to cold or lifted about, she became very deeply cyanosed.

The heart murmur heard at first examination was not heard again for about a month. It never became constant, and when heard it was never transmitted to the neck and no thrill was ever felt.

Death occurred May 2, 1916, when the girl was about 9 months of age, following two severe convulsions.

Necropsy.—When the chest was opened it was seen that the left lobe of the thymus was quite large, the tip being in the fourth interspace, the extreme left edge being 2½ cm. to the left of the midsternal line.

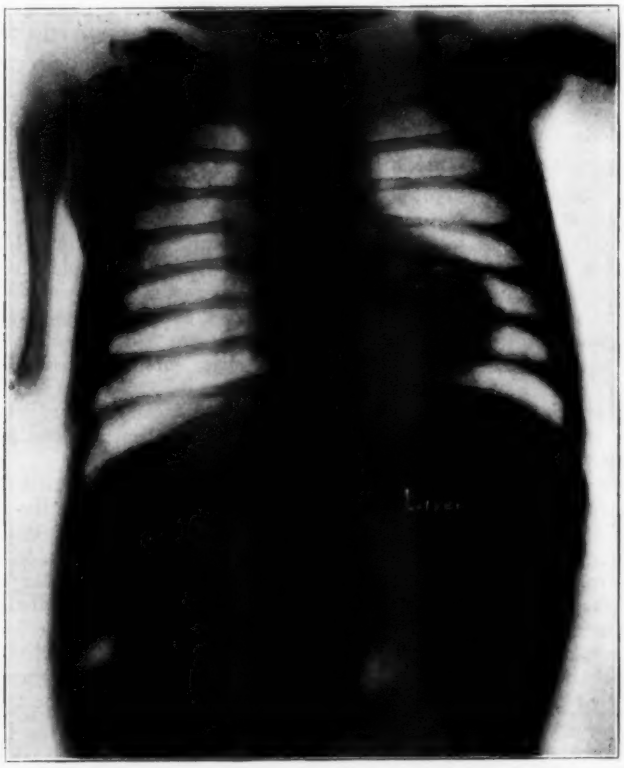

Fig. 1.—Roentgenogram showing dextrocardia.

The heart was on the right side, the lungs, including the lobar divisions, were normal. The liver, stomach and spleen were in normal position and without abnormalities. The pericardium contained 18 c.c. clear fluid. The heart was globular in shape, the walls of the left ventricle very thick, those of the right rather thin, with a muscular defect which showed as a dimple in the external surface, not extending through the wall. The heart valves were normal except for the patent ductus ovale. There was no interventricular defect. The large vessels leading off from the rather exaggerated aortic arch were in normal position.

Thanks are due to H. H. Dachtler for the Roentgen-ray work and to W. E. Mosely for the necropsy.

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PYELITIS OF INFANCY

I. MODE OF INFECTION *

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There have been two antagonistic theories advanced to explain the mode of the infection of the kidney in pyelitis of infancy. One theory maintains that the infection of the kidney takes place by the ascending route, through urethra, bladder and ureters; the other, that the infection comes by means of the blood and lymphatics. Before discussing the relative merits of these two theories certain facts in regard to pyelitis as it occurs in infants need to be noted. The disease is much more common in girl than in boy infants, the proportion being nearly three to one. The organism most frequently causing the disease is the colon bacillus, which is the offender in from 50 to 90 per cent. of cases. The pathology of the condition is well established. In uncomplicated cases the pelvis of the kidney is the only portion of the urinary tract involved, and there the local lesion is simply a low grade inflammation. The ureters and bladder are normal. Many cases show in addition some degenerative changes in the kidney substance, due to extension of the process inward from the pelvis. When the tissues are invaded by pus-forming cocci, there is secondary abscess formation.

With these facts as a basis, those who believe in the ascending route of infection argue that the colon bacillus enters the urethra, ascends against the urinary stream and, causing no lesions in its progress, localizes in the pelvis of the kidney and by its growth there gives rise to disease. This theory gains its greatest support from the large proportion of cases among girls, who, theoretically with a short urethra and of easy contamination with fecal matter, become more readily infected. There is very little experimental work in its support. Bond[1] showed that in the intestine, fallopian tubes and biliary passages solid particles may be carried upward by a current hugging close to the surface, and that in the ureter, when no urine is coming down, this

* Submitted for publication May 18, 1916.
* From the Children's Medical Department, Massachusetts General Hospital.
* Read at the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

1. Bond: Med. Rec., New York, 1905, lxviii, 246.

passage upward may also occur. Many others[2] state the opinion that ascending infection may occur in some or all cases, but they have no sure evidence to support the belief.

Directly against the ascending method of infection are the facts that colon bacilli have never been shown to pass up the normal, unobstructed ureter and that the colon and tubercle bacilli have been introduced repeatedly into the bladder and in the presence of a normal mucous membrane are excreted without causing damage of any kind.[3] Ascending infection occurs only in the presence of obstruction to the outflow of urine and cannot occur if the sphincter of the ureter is normal.[4] It seems to me that the ascending theory of kidney infection so far as it applies to the pyelitis of infancy has not been proved and the facts are against it.

The theory of kidney infection by the blood and lymphatics rests upon much surer ground. The work of Thiele and Embleton[5] seems to show that bacteria may pass to the kidney by the lymphatics alone, appearing first in the fat capsule and being distributed through the kidney also by the lymphatics. If bacteria appear in the urine, that is, if they have passed through the kidney, they must have reached the kidney by the blood stream. This latter procedure is what occurs in pyelitis, so we must have had a blood infection.

The direct lymphatic connection as shown by Franke[6] between the colon and the right kidney, which is the kidney most frequently affected in unilateral infection, has led some writers[7] to believe that bacteria pass directly from the intestine to the kidney by these lymph

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2. Among these may be cited the following:
Thomas, J.: Lancet, London, 1913, ii, 467.
Wright: Practitioner, London, 1909, lxxxii, 344.
McCrea: Practitioner, 1910, lxxxv, 346.
Wyman: Boston Med. and Surg. Jour., 1914, clxx, 540.
Freeman: Jour. Am. Med. Assn., 1914, lxiii, 1802.
Cunningham: Jour. Am. Med. Assn., 1915, lxiv, 231.
Heubner: Jahrb. f. Kinderh., 1913, lxxvii, 1.
Ross: Lancet, London, 1915, i, 654.
Shaw: Clin. Jour., 1908, xxxi, 273.
Box: Brit. Med. Jour., 1910, ii, 1128.
Barnard: Lancet, London, 1905, ii, 1243.
Herringham: Clin. Jour., 1909-1910, xxxv, 241.
Sampson: Bull. Johns Hopkins Hosp., 1903, xiv, 334.

3. Leutscher: Bull. Johns Hopkins Hosp., 1911, xxii, 361. Bauereisen: Ztschr. f. gynäk. Urol., 1910, ii, 132.

4. Rovsing: Sixteenth International Medical Congress, Budapest, 1909.

5. Thiele and Embleton: Proc. Roy. Soc. Med., Path. Sec., 1913-1914, vii, 69.

6. Franke: Mitt. a. d. grenzgeb. d. Med. u. Chir., 1911, xxii, 623; Ibid., 1911, xlviii, 1973.

7. Wilson: Brit. Jour. Child. Dis., 1913, x, 289. Jeffrey: Quart. Jour. Med., 1910-1911, iv, 267.

vessels—the so-called transparietal route. This probably occurs, but gives rise to an infected kidney, not to pyelitis as we see it in infants. Pyelitis may follow this condition by secondary blood infection.

The usual mode of infection in pyelitis appears to be somewhat as follows: From the intestinal tract or some other source bacteria get into the lymphatic vessels and then into the blood, or possibly directly into the blood. They are transferred by the blood to the kidney. After reaching the kidney they pass through the glomeruli and are excreted at the pelvis. They may pass out of the body in the urine without doing any damage, or they may set up an infection at their point of excretion, that is, produce a pyelitis. They may during their passage through the kidney cause more or less damage to the various portions of the organ. Which of the alternatives occurs within the kidney depends on the virulence and character of the bacteria and on the resistance of the individual and of the local tissues. The colon bacillus, being of comparatively low pathogenicity, causes almost no damage to the kidney substance in its passage through the organ. An infection of the kidney may take place by extension inward from the pelvis, probably by lymphatic channels. This infection causes a greater or less degree of permanent damage to the substance of the kidney and presents a complication of, or sequel to, the usual pathology of the disease. The various stages in this process as outlined in the foregoing statement have been well established.

Blood infection in nearly all the acute infectious diseases is now so well known that no proof needs to be given in its support. The colon bacillus has been found in the blood by several investigators.[8] Crabtree found that organism in the blood in seven out of nine patients who developed pyelitis under observation. The blood infection was always early in the disease, disappearing later, as in typhoid fever.

The intestinal tract is the most likely source of the infection in the majority of cases of pyelitis, especially in those due to the colon bacillus. Calmette[9] and many others[10] have shown that pigment par-

8. Crabtree: Lancet-Clinic, 1916, cxv, 96. Moser: Deutsch. Ztschr. f. Chir., 1915, cxxxii, 71. Ruediger: Philippine Jour. Sc., 1915, x, 25.

9. Calmette: Ann. de l'Inst. Pasteur, 1905, xix, 601; Ibid., 1906, xx, 353, 609; Compt. rend Soc. de biol., 1906, lxi, 161, 548.

10. Among these may be cited the following:
Arbeiter: Virchows Arch. f. path. Anat., 1910, cc, 321.
Whitla and Symmers: Brit. Med. Jour., 1908, ii, 61.
Nichols: Jour. Med. Research, 1904, xii, 455.
Ford: Tr. Assn. Am. Phys., 1900, xv, 389.
Adami: Montreal Med. Jour., 1898, xxvii, 485; 1902, xxxi, 105.
Cobbett: Jour. Path. and Bacteriol., 1910, xiv, 563.
Griffith: Royal Commission on Tuberculosis, Second International Report, 1907, Appendix 1, 628, 696.
Ravenel: Jour. Med. Research, 1903, x, 460.
Ravenel and Reichel: Jour. Med. Research, 1908, xviii, 1.

ticles, tubercle bacilli and other bacteria are carried with the fat from the intestinal canal in the lymph vessels of the mesentery during digestion and are distributed by the blood to all parts of the body, including the kidney. Other writers have called attention to the passage of the colon bacillus through the damaged intestinal mucous membrane,[11] and to the frequent association of pyelitis with constipation and other digestive disturbances.[12] Ten Broeck[13] found organisms of the colon bacillus group post mortem in the heart's blood of five out of fourteen patients dying of infectious diarrhea and in the ileocecal lymph nodes in five cases. Trumpp[14] found colon bacilli in the urine of fourteen out of seventeen children with follicular enteritis. Morse[15] and Knox[16] include cases of pyelitis in their reports of urinary analyses in gastro-intestinal diseases. Kowitz[17] has emphasized the seasonal incidence of pyelitis following the diarrheas of summer. Edith Williams[18] found in urine cultures of seventy consecutive cases that of forty-four patients with chronic intestinal disorders, sixteen showed colon bacilli. The importance of considering the gastro-intestinal tract in the treatmen of pyelitis has been emphasized by many writers[19] and is well known to all who have had experience with the disease. MacGowan[20] says he has seen a direct rise and fall of the bacilli in the urine with the neglect or care of the bowels.

Undoubtedly, there are sources of infection other than the gastro-intestinal tract, such as the teeth, tonsils and local septic lesions. Several writers[21] have emphasized this and the necessity of finding and

11. Park: Tr. Am. Surg. Assn., 1893, xi, 213. French: Brit. Med. Jour., 1908, i, 1029. Thiemich: Jahrb. f. Kinderh., 1910, lxxii, 243.

12. Brennemann: Jour. Am. Med. Assn., 1911, lxi, 631. Friedenwald: Arch. Pediat., 1910, xxvii, 801. Dudgeon: Lancet, London, 1908, i, 615. Green: Boston Med. and Surg. Jour., 1913, clxviii, 645. Cannato and Caronia: Pediatria, 1914, xxii, No. 9. Langstein: Med. Klin., 1913, ix, 1491. Zobel: Jour. Am. Med. Assn., 1916, lxvi, 496. White, W. H.: Lancet, London, 1912, ii, 1204.

13. Ten Broeck: Boston Med. and Surg. Jour., 1915, clxxiii, 284.

14. Trumpp: Jahrb. f. Kinderh., 1897, xliv, 268.

15. Morse and Crothers: Arch. Pediat., 1909, xxvi, 561.

16. Knox and Meakins: Arch. Int. Med., 1908, ii, 241.

17. Kowitz: München. med. Wchnschr., 1914, lxi, 1341.

18. Williams, E.: Lancet, London, 1912, ii, 511.

19. Among these may be cited the following:
Pardoe: Brit. Med. Jour., 1910, ii, 1129.
Briscoe: Lancet, London, 1909, ii, 1269.
Hutchinson: Clin. Jour., 1911, xxxviii, 209.
Thompson, W. H.: Med. Rec., New York, 1910, lvii, 907.
Pringle: Practitioner, London, 1911, lxxxvii, 35.
Jeffreys: Quart. Jour. Med., 1911, iv, 267.

20. MacGowan: Jour. Am. Med. Assn., 1915, lxiv, 226.

21. Rawles: Med. Rec., New York, 1911, lxxx, 707; Ibid., 1912, lxxxi, 359. Smith, F. H.: Old Dominion Jour. Med. and Surg., 1914, xix, 77. Nice: South. Med. Jour., 1915, viii, 1027. Grulee and Gaarde: Jour. Am. Med. Assn., 1915, lxv, 312. Huet: Nederl. Tijdschr. v. Geneesk., 1916, p. 521, abstr. Jour. Am. Med. Assn., 1916, lxvi, 993.

removing the source of infection. The extra-intestinal sources are especially important in those cases in which the organism is some other than the colon bacillus. A patient of mine well illustrates this point: An infant 2 days old had a high temperature, a few impetiginous pustules on the neck and a pyelitis. The organism in the pustules was *Staphylococcus aureus* and the same organism was in the urine. After the healing of the skin lesions the pyelitis quickly disappeared.

The work of Kraus[22] has shown definitely that bacteria may pass through the kidney without causing lesions in its substance. If staphylococci are injected into the ear of a rabbit, they cause lesions in the heart, abdominal wall and pyramids of the kidney passing through the glomeruli without setting up inflammation. Honeij[23] found leprosy bacilli in the urine of patients during the febrile stage of the disease. Brown,[24] Rist and Kindberg[25] and Foulerton and Hillier[26] found tubercle bacilli in the urine of patients whose kidneys were not damaged. Crabtree has injected the paratyphoid organism into the rabbit and recovered it from the urine. At necropsy the kidneys were normal.

The infection of the pelvis of the kidney from within, that is, by bacteria brought to it by the blood and excreted, seems established.

The possibility of the infection of the kidney substance from infection in the pelvis was shown by Kumita,[27] who demonstrated the extensive lymphatic connection between all parts of the kidney. That such infection actually occurs has been demonstrated by Hugh Cabot and Crabtree[28] and supported by A. Müller.[29]

This statement of the mode of infection in pyelitis satisfies all the conditions except in offering an explanation for the greater frequency of the disease in females. This explanation is not hard to find, for no mention has been made of a very important source of lymphatic and blood infection of the kidney, namely, the pelvic organs. Poirier[30] and Sobotta[31] have shown that the lymphatic vessels draining the pelvic organs are connected by free anastomosis with the kidney. These vessels drain through the thoracic duct into the blood. Sweet and Stewart[32] proved experimentally that when the ureters were cut and sewed into the intestinal canal, if infection of the kidneys occurred,

22. Kraus: Arch. f. exper. Path. u. Pharmakol., 1896, xxxvii, 1.
23. Honeij: Jour. Infect. Dis., 1915, xvii, 376.
24. Brown, L.: Jour. Am. Med. Assn., 1915, lxiv, 886.
25. Rist and Kindberg: Presse med., 1914, xxii, 177.
26. Foulerton and Hillier: Brit. Med. Jour., 1901, i, 774.
27. Kumita: Arch. f. Anat. u. Path., Anat. Abt., 1900, xlix, 94.
28. Cabot, H., and Crabtree: Unpublished communication.
29. Müller: Ztschr. f. Urol., 1912, Supplement.
30. Poirier: The Lymphatics, Constable, London, 1903, Translation by Leof.
31. Sobotta: Human Anatomy, 1907.
32. Sweet and Stewart: Surg., Gynec. and Obstet., 1914, xviii, 460. Stewart: Univ. Penn. Med. Bull., 1910, xxiii, 233.

TABLE 1.—Detailed Record of the Cultures Made from the Secretions of the Vagina in Girls of Various Ages

Case	Age	No Growth	Staphylococci	Streptococci	Gram-Negative Bacilli	Colon	Other Organisms
1	2 hours.....	+					
	30 hours.....	..	+	..	+		
2	6 hours.....	+					
	34 hours.....	..	+				
3*	6 hours.....	..	..	+			
	6 hours.....	..	..	+			
	13 days.....	..	+	+	+		
4	22 hours.....	..	..	+			
5	7½ hours.....	+					
	8 days.....	..	+	+			
6	2 days.....	..	+				
	11 days.....	..	+	+	+		
7	3 days.....	..	+	..	..	..	Spore bearing gram. neg. bac.
8	4 days.....	..	+	..	+		
	9 days.....	..	+	..	+		
9	2½ hours..... ..	+					
	2 days.....	..	+	..	+		
	5 days.....	..	+				
	8 days.....	..	..	+			
10	7 hours.....	+					
	3 days.....	..	+	+	..	..	Gram positive bac.
	6 days.....	..	+				
11	8 days.....	..	+				
12	2 days.....	..	+				
	5 days.....	..	+	..	+		
	8 days.....	..	+	..	..	+	
13	18 hours.....	..	+	+			
	4 days.....	..	+	+			
14	7 hours.....	+					
	3 days.....	..	..	+			
15	2 days.....	..	+	..	+		
	5 days.....	..	+				
16	24 hours.....	+					
17	3 years.....	..	..	+			
	3 years.....	..	..	+			
	3 years.....	..	..	+			
	3 years.....	..	..	..	+		

* Secretion taken from the vulva. † Secretion taken from the urethra.

TABLE 1.—Detailed Record of the Cultures Made from the Secretions of the Vagina in Girls of Various Ages—(*Continued*)

Case	Age	No Growth	Staphylococci	Streptococci	Gram-Negative Bacilli	Colon	Other Organisms
18	8 months.....	..	..	+	+		
	8 months.....	..	+	..	..	+	
19	6 years.....	..	..	..	..	..	Gram negative diplococcus
	6 years.....	..	..	+			
	6 years.....	..	..	+	..	..	Gram negative diplococcus
†	6 years.....	..	..	..	..	..	Gram negative diplococcus
20	2 years.....	..	..	+	+		
	2 years.....	..	..	+	+		
21	8 years.....	..	+				
22	8 years.....	..	..	+			
23	2 months.....	..	..	..	..	+	
24	6 months.....	..	+	+	..	+	
	6 months.....	..	..	..	..	+	
	6 months.....	..	..	..	..	+	
25	5 years.....	..	..	..	+		
26	16 months.....	..	..	..	..	+	
27	3 months.....	..	..	..	..	..	Bacillus fluorescens?
28	4 months.....	..	..	..	..	..	Bacillus fluorescens?
29	3 weeks.....	..	..	+			
30	1 week.....	..	+	+			
31	6 days.....	+					
32	6 days.....	..	+	+			
33	5 days.....	..	..	..	..	+	
34	5 years.....	..	..	..	..	+	
*	5 years.....	..	..	..	..	+	
35	2 years.....	..	..	..	..	+	
†	2 years.....	..	..	+			
36	11 months.....	..	+	+			
†	5 years.....	..	+	+			
37	8 months.....	..	+	+			
	5 years.....	..	..	+			
38	7 months.....	..	..	..	..	+	
39	4 months.....	..	..	..	..	+	
40	3 weeks.....	..	..	..	+		
	Total.....	8	29	29	14	13	

* Secretion taken from the vulva. † Secretion taken from the urethra.

it was through the lymphatics about the ureters not through the lumen of the ureter. Sakata,[33] Sugimura,[34] Bauereisen,[3] J. Thomson,[35] W. B. Clarke,[36] and Eisendrath and Kahn,[37] working on the problem of kidney infection, all come to the same conclusion, that the lymphatics, not the ureters, play the major rôle in conveying direct infection from the pelvic organs to the kidney. If bacteria get into the lymphatics, they may get into the blood through the thoracic duct and thus to the kidney, or possibly into the blood from the infection in the kidney, and cause a pyelitis. Thiele found bacteria in the blood and urine from pelvic infection. Cases of pyelitis following circumcision have been reported by many writers. Rovsing[38] in 1897 reported several cases of pyelitis in young married women, following rupture of the hymen. The female genital organs, with the close proximity of the urethra, vulva and vagina to the rectum and the semi-closed character of the parts, offer every advantage for the entrance and growth of colon bacilli and other bacteria.

To see whether this region was in fact a possible source of infection, I have made seventy-one cultures from the vagina, vulva or urethra of forty infants and young children. One infant 6 hours old and all over 18 hours old, except one infant 6 days old, showed a growth from vaginal culture. All the vulval and urethral cultures were positive. The first organisms to appear were streptococci and staphylococci and then small bacilli—not colon. Colon bacilli were found in vaginal cultures of infants as early as the fifth day.

The colon bacillus was identified by the following characteristics: motile bacillus, gram negative, obtained from characteristic (shiny, dirty, brown, confluent) colony on agar, giving acid coagulation of litmus milk, forming gas in glucose, and producing characteristic (as above) growth on potato.

The other bacillus frequently found was delicate, nonmotile, gram negative, causing no change in litmus milk, forming no gas in glucose and easily outgrown even by streptococci.

These findings are in accord with Schmidgall,[39] who found the vagina of newborns sterile ten out of thirteen times, and by the second day a profuse growth of cocci. The colon bacillus was isolated twelve times out of twenty-one in newborns after the second day. She

33. Sakata: Arch. f. Anat. u. Physiol., Anat. Abt., 1903, 1.
34. Sugimura: Virchows Arch. f. path. Anat., 1911, xx, 206.
35. Thomson, J.: Quart. Jour. Med., 1909-1910, iii, 251.
36. Clarke, W. B.: Clin. Jour., 1911, xxxviii, 177. Walker: Lancet, London, 1913, i, 435.
37. Eisendrath and Kahn: Jour. Am. Med. Assn., 1916, lxvi, 561.
38. Rovsing: Ann. d. mal. d. org. génito-urin., 1897, xv, 897, 1009, 1121, 1251; Ibid., 1898, xvi, 179, 278.
39. Schmidgall: Beitr. z. Geburtsh u. Gynäk., 1914, xix, 190.

showed also that the vaginal secretions did not kill off the pathogenic organisms. Others[40] have found bacilli and cocci in the vagina and vulva of infants in differing proportions. Alsberg in adults found the colon bacillus in 100 per cent. of cases in the urethra of women and concludes that it is a regular habitant of the female urethra.

A possible source of infection with colon bacilli or other bacteria is certainly present in the female vulva, urethra and vagina, and a slight trauma might easily accomplish the entrance of organisms into the lymphatic vessels and blood and thus permit their transportation to the kidney.

I think that we have sufficient evidence to believe that pyelitis is always a blood infection and that the bacteria frequently gain entrance to the blood by the lymphatics. In the uncomplicated cases the lesion remains localized in the pelvis of the kidney, where the organisms are excreted. Secondary infection of the kidney substance may occur by lymphatic channels from the pelvis. Quite possibly these secondary infections account for many "relapses." The source of the infection in the majority of cases, considering males and females together, is the gastro-intestinal tract. Some cases may arise from infection in the skin, teeth or tonsils or in some local septic process. Many cases in females, accounting for the greater number in this sex as compared with the males, arise from bacteria entering the blood, often via the lymphatics, from the urethra, vulva or vagina,

I wish to express my thanks to Dr. Franklin S. Newell for his kindness in permitting me to make cultures from infants at the Boston Lying-In Hospital, and to Dr. Richard S. Eustis and Dr. John W. Hammond, Jr., for assistance in the laboratory.

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40. Among these may be cited the following:
Menge: Deutsch. med. Wchnschr., 1894, xx, 867.
Strognoff: Monatschr. f. Geburtsh u. Gynäk., 1895, ii, 365.
Vahle: Ztschr. f. Geburtsh u. Gynäk., 1895, xxxii, 368.
Knapp: Monatsch. f. Geburtsh u. Gynäk., 1897, v, 84.
Neujean: Beitr. z. Geburtsh u. Gynäk., 1906, x, 408.

41. Alsberg: Arch. f. Gynäk., 1910, xc, 255.

ACETONE BODIES IN THE BLOOD OF CHILDREN*

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DES MOINES

In the literature of recent years many articles are to be found relating to acidosis, acetonuria, and acetonemia in children. These terms frequently are used synonymously, and many widely different conditions are described under these headings. In all reports of acetonemia that I have found various conditions are described in which the urine is characterized by the presence of acetone and diacetic acid. With the exception of Marriott's[1] papers I have found no records of the determination of acetone bodies (beta-oxybutyric acid, aceto-acetic acid, and acetone) in the blood of living children. This work was undertaken to determine the amount of acetone bodies in the blood of normal children and of children in various pathologic conditions, especially those with evidence of acidosis, such as, increased pulmonary ventilation, decreased carbon dioxid tension of the alveolar air, diminished alkali reserve of the blood serum and abnormal acidity of the urine.

The analyses of the blood were made according to Marriott's[1] modification of Shaffer's oxidation method for determining acetone bodies in the urine. One cubic centimeter of blood is sufficient for accurate estimation. The results are expressed in milligrams of acetone per 100 gm. of blood. In some cases the acetone bodies in the urine were also determined and the results are expressed in grams of acetone. When sufficient quantities of urine were available, the acetone was estimated as in Shaffer's method.[2] When only small quantities were available, the urine was oxidized in the usual way and the reading made in the nephelometer, as in the blood analyses.

In Table 1 are the findings in sixteen normal children, arranged according to their ages. These were dispensary patients suffering from a variety of minor troubles and were essentially normal as far as their nutrition was concerned. All were afebrile when the blood was taken. The ages varied from 5 weeks to 5 years. The average total acetone content of the blood was 6.3 mg. per 100 gm. The minimum quantity found was 0.8 mg. and the maximum was 13 mg. These extremes speak for the variation in the normal child. Marriott[1] reported deter-

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* From the Harriet Lane Home and from the Department of Pediatrics of the Johns Hopkins University.

1. Marriott: Jour. Biol. Chem., 1913, xvi, 293; Ibid., 1914, xviii, 507.
2. Shaffer: Jour. Biol. Chem., 1908, v, 211.

minations of acetone bodies in the blood of six normal children from 5 to 10 years of age. He found an average total of 3.7 mg. per 100 gm.

TABLE 1.—ACETONE BODIES IN THE BLOOD OF NORMAL CHILDREN EXPRESSED AS MILLIGRAMS IN 100 GRAMS

Case Number	Age	Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total Acetone Bodies	Beta Ratio	Remarks
1	5 wk	2.5	4.4	6.9	63	Breast fed
2	6 wk.	1.4	1.3	2.7	48	Breast fed
3	7 wk.	0.3	0.5	0.8	62	Breast fed
4	11 wk.	0.7	0.6	1.3	46	Breast fed
5	4 mo.	2.1	1.2	3.3	33	Mixed feeding, breast and cow's milk
6	4 mo.	2.0	11.0	13.0	84	Mixed feeding
7	6 mo.	0.8	1.1	1.9	57	Mixed feeding
8	6 mo.	2.7	5.4	8.1	66	Breast fed
9	16 mo.	1.9	1.4	3.3	42	General diet
10	2 yr.	1.4	1.9	3.3	58	General diet
11	2½ yr	3.9	8.8	12.7	69	General diet
12	3 yr.	1.8	3.0	4.8	62	General diet
13	3 yr.	3.7	5.6	9.3	60	General diet
14	3 yr.	3.9	3.6	7.5	48	General diet
15	3 yr.	5.3	6.8	12.1	56	General diet
16	4 yr.	4.0	5.8	9.8	60	General diet
Minimum.....		0.3	0.5	0.8	33	
Maximum.....		5.3	11.0	13.0	84	
Average.....		2.4	3.9	6.3	57	

Starvation has long been recognized as a cause of acetonuria. The frequency of the acetone reaction in the urine of children with widely differing diseases indicates the mild degree of metabolic disturbance which may cause the excretion of acetone bodies. For example, Frew[3] reported that from 60 to 65 per cent. of the urines of 662 patients admitted consecutively to the Great Ormond Street Hospital gave positive tests for acetone when examined by the sodium nitroprussid test, according to Rothera's[4] method. He concluded that the disease from which the child was suffering had less to do with the appearance of acetone bodies than the dietetic changes incident to admission to the ward. The latter are especially important because

3. Frew: Lancet, London, 1911, ii, 1264.
4. Rothera: Jour. Physiol., 1908, xxxviii, 491.

of the large number of children who are partly or completely starved for a time after admission, either through voluntary refusal or restricted feeding.

One case afforded me an opportunity to estimate the blood acetone in a normal starving infant. A normal child of 20 months who had refused everything except the breast was admitted to the hospital to be weaned. She had been exclusively breast fed and refused all food for forty-eight hours after admission. After two days of voluntary starvation the blood was examined and found to contain 39.5 mg. of acetone bodies per 100 gm. of blood. The child was irritable, but there were neither signs of disease nor evidence of acidosis.

The results in six cases of marked eczema are recorded in Table 2. These children ranged from 1 month to 3 years of age. One child of 3 years had a very small amount, 1.3 mg. per 100 gm.; another, 8 months of age, showed an amount equal to that of the normal nursling, that is, 5.2 mg. per 100 gm. The others showed some increase, giving an average of 10.3 mg., a little less than twice the normal.

TABLE 2.—ACETONE BODIES IN THE BLOOD OF CHILDREN WITH ECZEMA EXPRESSED AS MILLIGRAMS PER 100 GRAMS

Case Number	Age	Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total Acetone Bodies	Beta Ratio	Remarks
17	1 mo.	4.8	12.5	17.3	72	Breast fed 2 weeks; condensed milk 2 weeks
18	5 mo.	3.6	6.2	9.8	63	Fed on cow's milk formula
19	8 mo.	7.4	9.1	16.5	55	
20	8 mo.	1.7	3.5	5.2	67	Died within 12 hrs. after blood was taken
21	2½ yr.	6.7	...	...	..	Had had eczema constantly since 1 month of age
22	3 yr.	0.6	0.7	1.3	53	
Average.....		4.1+	6.4	10.5	62	
Minimum.....		0.6	0.7	1.3	53	
Maximum.....		7.4	12.5	17.3	72	

Table 3 includes five cases of acute infection with marked febrile reaction. It has long been recognized that with acute infectious diseases it is the rule to find acetone bodies in the urine. Their presence is so uniform that it is of no service in differential diagnosis. The amount determined by urinary analysis is not large, and, contrary to the opinion which was entertained at one time, it is now believed that the acetonemia does not add to the severity of the disease. This belief is justified by the findings that I have obtained in three cases of pneumonia, one of

TABLE 3.—Acetone Bodies in the Blood of Children with Acute Febrile Disease Expressed as Milligrams Per 100 Grams

Case Number	Age	Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total Ace-tone Bodies	Beta Ratio	Clinical Diagnosis	Remarks
23	11 mo.	6.9	15.0	21.9	68	Pneumonia.....	Temperature, 104; blood examined on fifth day; uneventful recovery
24	1 yr.	7.2	15.4	22.6	66	Pneumonia.....	Fatal result
25	3 yr.	5.0	18.0	23.0	78	Empyema.....	Recovery
26	2 yr.	7.8	5.7	13.5	42	Pneumonia with acidosis	Blood examined before alkali administration; rapidly progressive to fatal termination
26	2 yr.	3.4	13.6	17.0	80	.....	Alkali intravenously; blood taken 15 minutes after respiration ceased; 35 c.c. urine contained 30 mg. acetone bodies
27	6 mo.	1.8	9.6	11.4	84	Pyelonephritis.....	Necropsy: Multiple abscesses of both kidneys

empyema and one of pyelonephritis. The acetone bodies were increased but not to a degree sufficient to cause clinical symptoms or laboratory findings pointing to acidosis. Nor was the amount sufficient to interfere in any way, so far as can be demonstrated at the present time, with metabolic processes. All the children (except the child in Case 26, Table 3) were taking food but an amount rather less than usual. The febrile reaction temperature varied from 103 to 105 F. It is noteworthy that three of the patients with pulmonary disease had nearly the same amount of acetone bodies and that this was much less than that found in the afebrile patient suffering from voluntary starvation. Case 24 terminated fatally. Case 26 gave evidence clinically of acidosis, as indicated by an increased pulmonary ventilation, which was corroborated by the demonstration of an increased hydrogen ion concentration in the blood serum and a decreased alkalinity of the blood as shown by Sellards' test. The acetone bodies in this patient, however, were very slightly increased. They were less than in the other patients with pneumonia which presented no evidence of acidosis. The child passed only 35 c.c. of urine during the twelve hours that he was in the hospital. This contained approximately 1 mg. of acetone bodies per cubic centimeter of urine. The amount of these bodies was not sufficient in any way to account for the marked evidences of acidosis that he presented. The acidosis must have been due to an accumulation in the blood of other acids. The course of the disease was rapidly progressive and the patient died about twelve hours after admission.

The cases included in Table 4 were cases of diarrhea. Six of the children were suffering from diarrhea with acidosis of the type described by Howland and Marriott.[5] The acetone bodies in the blood were increased in all of these cases but only moderately so (11.1, 35, 10.2, 19 and 21.3 mg. per 100 gm. blood). This increase of the acetone bodies in such cases probably plays a minor part in the production of acidosis. This is well shown by the fact that other patients with diarrhea, but with no evidence of acidosis by laboratory tests, had quite as high an acetone body content in the blood. The table demonstrates this. Thus, the results of analyses in four cases were 14.4, 15.7, 22.8 and 30.3 mg. per 100 gm. of blood. With ileocolitis, on the other hand, I have found, in at least two cases, a large amount of acetone bodies in the blood. With one child the amount varied greatly from day to day. The large amount of 138.6 mg. per 100 gm. was determined on one occasion. Until further observations have been made it is impossible to say whether the increase in ileocolitis is due merely to the greater prolongation of an insufficient diet or whether something of a more specific nature plays a rôle.

5. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 63.

TABLE 4.—Acetone Bodies

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone				Remarks
			Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio	
28	8 mo.	5/29	2.3	8.8	11.1	77	Diarrhea with acidosis	.....	.....	.....	..	Urine negative for acetone
29	7 mo.	6/ 7	11.0	24.0	35.0	68	Diarrhea with acidosis	0.012	0.019	0.031	61	Before giving alkali
29	7 mo.	6/ 8	....	....	....	..	.....	0.045	0.088	0.133	60	After giving alkali
30	15 mo.	7/20	4.4	5.8	10.2	56	Diarrhea with acidosis					
31	7½ mo.	7/15	....	....	22.0	..	Diarrhea with acidosis					
32	6 mo.	6/13	....	....	21.3	..	Diarrhea with acidosis					
33	3 mo.	8/ 5	....	....	19.0	..	Diarrhea with acidosis					
34	10 mo.	11/13	....	....	14.4	..	Fatal diarrhea without acidosis					
34a	22 mo.	7/10	....	....	15.7	..	Fatal diarrhea without acidosis					
35	7 mo.	7/ 6	....	....	22.8	..	Fatal diarrhea without acidosis					
36	5 mo.	7/ 2	....	....	30.3	..	Fatal diarrhea without acidosis					
37	2 yr.	3/13	16.7	11.9	28.6	41	Ileocolitis.....	0.198	0.700	0.898	77	Urine in 20 hr., 130 c.c. before alkali
37	2 yr.	3/14	....	....	....	..	.....	0.333	1.275	1.608	79	Urine in 12 hr., 140 c.c.; alkali treatment
37	2 yr.	3/16	72.6	66.0	138.6	47	.....	1.776	4.675	6.451	72	Urine in 20 hr., 450 c.c.; 140 mg. acetone per 100 c.c. urine
37	2 yr.	3/17	....	....	....	..	.....	0.633	1.735	2.368	73	Urine in 20 hr., 250 c.c.
37	2 yr.	3/18	....	....	....	..	.....	2.356	5.682	8.038	70	Urine in 24 hr., 515 c.c.
37	2 yr.	3/19	58.7	52.1	110.8	47	.....	1.520	3.363	4.883	68	Urine in 18 hr., 410 c.c.; 110 mg. acetone per 100 c.c.
37	2 yr.	3/23	52.8	23.7	76.5	30						
38	8 mo.	4/16	7.4	9.1	16.5	55	Ileocolitis.....	.. ..	.....	.....	..	Acetonuria
38	8 mo.	4/17	51.7	130.9	182.6	71	.....	0.051	0.160	0.211	75	Urine in 28 hr., 45 c.c.

Table 5 shows that in the cases with which there is apparently a spontaneous formation of acetone bodies the amount of these found in the blood is often large. One child of 3 years, who died after an illness of only seventy-two hours, had 170 mg. per 100 gm. of blood. Another, of 3 years, with 88 mg. per 100 gm. of blood recovered after an illness of five days, while a third, 14 months old, who had been ill for three days, died. On the third day of illness he had 136 mg. of the acetone bodies per 100 gm. of blood. The amount is thus seen to be greatly in excess of that found with ordinary acute diseases and approaches closely to the amount (240 mg.) that I found in a fatal case of diabetic coma in an adult. The mechanism for the rapid formation of the acetone bodies in these apparently spontaneous cases is quite unknown and cannot even be suggested at present.

Two cases of diabetes mellitus (Table 6) in boys of 3 and 8 years afforded opportunity to make parallel determinations of the blood acetone and the acetone bodies excreted in the urine. Both showed very mild symptoms of acidosis when admitted. They responded quickly to starvation treatment. They rapidly became sugar free and showed a marked reduction in the acetone output. The younger boy proved to have a more severe form of diabetes and his blood acetone did not diminish under treatment as did that of the other. As the diet was increased his blood acetone increased almost to the original amount, while that of the older boy was reduced from 50 to 20 mg. They show well that the amount of acetone bodies in the blood does not bear any constant relation to that excreted in the urine. On April 1 the blood acetone of the patient in Case 42 was 58.3 mg. and he excreted 3.674 gm., whereas the patient in Case 43 had a blood acetone of 50.9 mg. and excreted only 1.408 gm. acetone in the urine. On April 9 there was 10 per cent. difference in the amount of acetone bodies excreted while the difference in the blood was 50 per cent. On April 14 the patient in Case 42 had 2.7 times as much acetone bodies in the blood as the patient in Case 43 but his excretion of acetone bodies was actually less. Comparison of the blood acetone and urinary acetone of the same patient at different times also illustrates this fact. In considering the constantly increased blood acetone of the patient in Case 42, it should be stated that his tolerance for food was much less than that of the older patient. Neither of these patients presented any signs of acidosis after the first few days in the ward.

Neubauer[6] first called attention to the proportion of beta-oxybutyric acid in the urinary excretion in some work on experimental acidosis and diabetic urines. This is expressed as the percentage of the total

6. Neubauer: Verhandl. d. deutsch Kong. f. inn. Med., 1910, xxvii, 566.

TABLE 5.—Acetone Bodies

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone				Remarks
			Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio	
37a	3 yr.	4/17	29.9	140.1	170.0	82	Recurrent vomiting...	0.086	0.205	0.291	70	Urine in 20 hr., 70 c.c.; fatal
38a	3 yr.	1/18	....	....	....	..	Renal tumor with spontaneous aceto-naemia	2.472	6.428	8.9	72	Incomplete 24 hr. specimen, 620 c.c.
39	14 mo.	1/ 9	....	....	136.0	..	Spontaneous aceto-naemia	.....	.....	.....	..	Fatal
40	6 yr.	1/17	....	....	84.5	..	Recurrent vomiting...	.....	.....	.....	..	Rapid recovery
41	3 yr.	2/ 9	....	....	88.5	..	Spontaneous aceto-naemia	.....	.....	.....	..	Slow recovery

TABLE 6.—Acetone Bodies

Case No.	Age	Date	In the Blood, Expressed as Mg. Acetone per 100 Gm. Blood				Clinical Diagnosis	In the Urine, Expressed as Grams of Acetone				Remarks
			Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio		Acetone + Diacetic Acid	Beta-oxy-butyric Acid	Total	Beta Ratio	
42	3 yr.	3/30	....	....	....	..	Diabetes mellitus.....	1.364	3.685	5.049	73	General diet
42	3 yr.	4/ 1	25.3	33.0	58.3	56	.....	1.012	2.662	3.674	72	Green diet started
42	3 yr.	4/ 9	12.0	25.0	37.0	60	.....	0.363	0.737	1.100	66	60 gm. oatmeal added to green diet
42	3 yr.	4/14	8.3	44.0	52.3	84	.....	0.231	0.319	0.550	57	1 egg added to previous diet
43	8 yr.	3/30	....	....	....	..	Diabetes mellitus.....	0.913	2.470	3.383	73	General diet
43	8 yr.	4/ 1	20.9	30.0	50.9	60	.....	0.396	1.012	1.408	71	Green diet started
43	8 yr.	4/ 3	....	....	....	..	.....	0.429	0.286	0.715	40	
43	8 yr.	4/ 9	9.9	14.3	24.2	59	.....	0.380	0.620	1.000	62	60 gm. oatmeal added
43	8 yr.	4/14	7.9	11.6	19.0	61	.....	0.231	0.407	0.638	63	

acetone bodies in the urine and for convenience has been designated as the beta ratio. He observed that this ratio was from 60 to 80 per cent. in patients who were excreting several grams or more of acetone bodies. Others have given this point some consideration and recently Kennaway,[7] in analysis of diabetic urines, has corroborated Neubauer's observation. In a series of about twenty examinations of the urines of the two diabetics referred to above I have found the same thing. A striking example of this is shown in the urinary analyses in Case 43, recorded in Table 6, in which the beta ratio dropped from 71 to 40 with a decrease of total acetone bodies from 1.408 gm. to 0.715 gm. The subsequent rise of total acetone bodies to 1 gm. is accompanied by a beta ratio of 62. The beta ratio in other cases of acidosis bore no such relation. Excluding the patient moribund from pneumonia (Case 26) it was not less than 60 per cent. in any case, and was as high as 70 per cent. in some instances when the total acetone excretion was very small. The beta ratio in the blood acetone shows wide variations and permits no definite conclusions. In general I have been unable to attach any significance to the beta ratio in either the blood or the urine.

SUMMARY

The blood of sixteen normal children was examined quantitatively for acetone bodies (beta-oxybutyric acid, aceto-acetic acid and acetone). Expressed as milligrams of acetone per 100 gm. of blood, this was found to vary from 1 to 13 mg., with an average of 6.3 mg.

The blood of a normal child after forty-eight hours of voluntary starvation was examined for acetone bodies and found to contain 39.5 mg. acetone bodies per 100 gm. of blood.

Acute febrile disturbances are accompanied by an increase in the blood acetone, though this may not be very marked.

In some patients showing acidosis clinically, the acetone content of the blood was found to be sufficient to account for the acidosis.

Many cases of acidosis in infancy and childhood are not accompanied by an increase of acetone bodies in the blood sufficient to account for the severity of the acidosis.

In a given case of acidosis acetonuria alone does not indicate that the acidosis is due to an increase of the acetone bodies in the blood. To determine this quantitative studies of the blood are necessary.

Equitable Building.

7. Kennaway: Biochem. Jour., 1914, viii, 355.

TYPES OF PNEUMOCOCCUS FOUND IN THE PNEUMONIAS OF INFANTS AND YOUNG CHILDREN*

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Immunologic studies have illuminated both bacteriology and serology by proving that the majority of pathogenic bacteria belong to groups composed of various types which may be identified by their reactions in the serum of infected animals. Dochez and Gillespie[1] showed that the pneumococcus group comprises four types which have since been found in Germany as well as in this country. Two additional types of pneumococci apparently exist in South Africa.[2] Types 1, 2 and 3 have definite immunity reactions identical to all members of the group, while Type 4 comprises a number of independent varieties differing from Types 1, 2 and 3 and also from each other. Pneumococci of Type 4 are ordinarily present in the mouth in healthy persons who have not been in contact with lobar pneumonia patients, and cause only 20 to 25 per cent. of the disease. While pneumococci of this type may be possessed of great virulence, cases of lobar pneumonia in adults caused by such cocci are but rarely fatal. By far the greater number of cases of lobar pneumonia (80 per cent.) are due to pneumococci belonging to Types 1, 2 and 3. Types 2 and 3 are responsible for the highest death rate, and Type 1 causes a lower percentage of fatalities than either of the other two.

Thus far studies on only adult patients have been made, and lobar pneumonia alone has been considered. The interesting question of the types of pneumococcus present in the pneumonias of infancy naturally suggested itself, and such a study was undertaken at the Babies' Hospital during the past winter.

TECHNIC

The method of obtaining material by puncturing the lung was not found practicable in young children, whose pulmonary consolidation may be small and superficial in extent, and the puncture attended with danger of causing pneumothorax. This method was therefore practiced in only three cases. For the rest, the sputum was relied on. The child was made to cough and the expectorated material was collected on a swab, rubbed up in salt solution and injected into a white mouse.

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* From the Pathologic Laboratory of the Babies' Hospital, New York.

1. Dochez and Gillespie: Jour. Am. Med. Assn., 1913, lxi, 727.
2. Dochez and Avery: Jour. Exper. Med., 1915, xxi, 114.

The animals were killed after twenty-four hours if they had not died within that time, and the necropsy was performed at once, cultures being made on blood agar from the peritoneal exudate and from the heart's blood. With the pure growths thus obtained agglutination tests were made with antipneumococcus serum kindly furnished us by the Rockefeller Institute Hospital. No more rapid technic was employed because no attempt was made to treat these children with specific antiserum and consequently no indication for haste existed.

CASES STUDIED

Fifty cases of respiratory disease were studied, the clinical diagnosis reading as follows:

Lobar pneumonia	11
Bronchopneumonia	36
Bronchitis	2
Postpneumonic empyema	1
Total	50

The age of the children varied from 25 days to 4½ years, as shown in the following tabulation:

Age	No.	Age	No.
Under one month	1	12 to 18 months	13
1 to 2 months	1	18 to 24 months	6
2 to 3 months	1	2 to 3 years	3
3 to 6 months	6	3 years	2
6 to 9 months	4	4½ years	1
9 to 12 months	12	Total	50

There were sixteen girls and thirty-two boys. The largest number of cases occurred during the month of December.

LOBAR PNEUMONIA

Analyzing the group of eleven lobar pneumonia patients, we find that the youngest was 6 months old and the oldest 3 years. Four were under 1 year, five were between 1 and 2 years and two were over 2 years of age. Four children died, all less than 18 months old.

LOBAR PNEUMONIA

CURED		IMPROVED	
Age, Mo.	No.	Age, Mo.	No.
36	1	30	1
20	1	DIED	
17	1	17	1
14	1	15	1
10	1	11	1
7	1	6	1

The pneumococci present in these eleven cases are shown in Table 1. It will be seen that a pneumococcus of Type 1 was found in three cases, Type 2 twice, and Type 4 seven times, while in two instances no pneumococci were found.

TABLE 1.—Bacteriologic Finding in Fifty Cases of Pneumonia

Case Number	Diagnosis	Organism	Source					Result			
			Sputum	Pleural Puncture	Blood	Lumbar Puncture	Necropsy	Cured	Improved	Unimproved	Died
46	Lobar pneumonia	Pneumococcus, Type 1 Pneumococcus, Type 4	+ ..	.. +	..	..	..	1			
43	Lobar pneumonia	Pneumococcus, Type 1 Pneumococcus, Type 4	+	+ +	+	..	..	..	..	..	1
35	Lobar pneumonia	Pneumococcus, Type 1 Pneumococcus, Type 4 Staphylococcus aureus	.. + +	..	..	..	+	..	..	..	1
45	Lobar pneumonia	Pneumococcus, Type 4	+	+	..	..	..	1			
10	Lobar pneumonia	Staphylococcus aureus Influenza	+ +	+	..	..	..	..	1		
1	Lobar pneumonia	Penumococcus, Type 2	+	..	..	..	..	1			
15	Lobar pneumonia	Penumococcus, Type 2 Influenza	+ +	..	..	..	..	1			
2	Lobar pneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	..	1
5	Lobar pneumonia	Pneumococcus, Type 4	+	.	..	..	..	..	..	..	1
22	Lobar pneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
6	Lobar pneumonia	Streptococcus (3 strains)	+	..	..	..	..	1			
29	Bronchopneumonia	Pneumococcus, Type 1	+	..	..	..	..	.	..	..	1
41	Bronchopneumonia	Pneumococcus, Type 1	+	..	..	..	..	..	..	..	1
8	Bronchopneumonia	Pneumococcus, Type 1 Staphylococcus aureus	.. ..	..	.	.	+ +	..	..	..	1
17	Bronchopneumonia	Penumococcus, Type 2	+	..	..	..	..	..	..	..	1
14	Bronchopneumonia	Penumococcus, Type 2	..	..	..	..	+	..	..	..	1
4	Bronchopneumonia	Penumococcus, Type 2 Streptococcus	+ +	..	..	..	..	1			
32	Bronchopneumonia	Penumococcus, Type 2 Influenza	+ +	..	..	..	..	1			
7	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	.	1
9	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
13	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
20	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	.	..	..	..	1	

25	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
27	Bronchopneumonia	Pneumococcus, Type 4	+	.	..	..	..	..	..	1	
28	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	..	1
37	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
38	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
40	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
42	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	..	1
44	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	..	1
47	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	..	..	..	1
50	Bronchopneumonia	Pneumococcus, Type 4	+	..	..	..	..	1			
3	Bronchopneumonia	Pneumococcus, Type 4	+	+	..	..	..	..	..	..	1
49	Bronchopneumonia	Pneumococcus, Type 4	+	+	.	..	..	..	..	1	
19	Bronchopneumonia	Pneumococcus, Type 4	+	..	+	+	..	..	..	..	1
18	Bronchopneumonia	Pneumococcus, Type 4	..	..	..	..	+	..	..	..	1
23	Bronchopneumonia	Pneumococcus, Type 4 Staphylococcus aureus	+ +	..	..	..	..	1			
16	Bronchopneumonia	Pneumococcus, Type 4 Influenza	+	..	..	..	..	..	..	..	1
24	Bronchopneumonia	Pneumococcus, Type 4 Influenza	+	..	..	..	..	..	1		
12	Bronchopneumonia	Streptococcus	+	..	..	..	..	1			
33	Bronchopneumonia	Streptococcus	+	..	..	..	..	1			
11	Bronchopneumonia	Staphylococcus aureus	+	..	..	..	..	..	..	..	1
30	Bronchopneumonia	Staphylococcus aureus	+	..	..	..	..	1			
48	Bronchopneumonia	Staphylococcus aureus	..	..	..	..	+	..	..	..	1
31	Bronchopneumonia	Influenza	+	..	..	..	+	..	..	..	1
39	Bronchopneumonia	Influenza	+	..	..	..	..	..	..	..	1
34	Bronchopneumonia	Influenza	+	..	..	..	..	..	..	..	1
21	Acute bronchitis	Pneumococcus, Type 4	+	..	..	..	..	1			
36	Acute bronchitis	Streptococcus	+	..	..	..	..	1			
26	Postpneumonic empyema	Pneumococcus, Type 4 Staphylococcus aureus	+ ..	.. +	..	..	.	..	1		
	Totals							21	3	3	23

The children from whom Type 1 pneumococci were isolated present several interesting facts. In the first place, two of three died, and all three presented a Type 4 pneumococcus in addition to the strain belonging to Type 1. Two of the three patients, one of whom recovered, developed purulent fluid in the pleural cavity and the pneumococcus isolated from the pleural fluid proved, in both instances, to be of a different type from that isolated from the sputum. Thus, in one child 14 months old the cocci present in the sputum belonged to Type 1, and those from the pleural exudate to Type 4. Recovery resulted. In a fatal case on the other hand, in a patient 21 months old, the sputum contained cocci of Type 4, while from the blood and pleural fluid cocci identified as belonging to Type 1 were isolated. In another fatal case the cocci in the sputum belonged to Type 4, but at the necropsy a Type 1 pneumococcus was found in the consolidated lung.

These two cases naturally raise the question as to whether sputum cultures in young children are reliable for a study of this kind; that is, whether the pneumococci found in the material obtained from the mouth are identical with those present in the pulmonary lesion. Do these young infants, in the weakened condition incidental to a severe pneumonia, make effectual efforts at coughing, and do they really raise sufficient pulmonary exudate to make cultural tests from mouth material a proper index of the cocci in the lung? That this is the rule in adults we know; that it does happen in infants is proved by one of our three cases, but that it does not always happen is shown by two other cases. It is certainly a fact to be taken into consideration, and lung puncture, when possible, should be chosen as the method to obtain a reliable specimen for study of the bacteriologic content of an area of pulmonary consolidation.

In the case in which the pleural pus contained Type 4 pneumococcus and the sputum Type 1, it is quite possible that some cocci of both types were present in both sputum and pleural fluid, but that the colonies fished for the agglutination tests did not agree. Since the morphology and the biology of pneumococci belonging to Types 1, 2 and 4 are identical, the only way to prove this point would be to fish a large number of colonies from the plates sown with the material from the mouse's blood and peritoneal exudate, and then study all such cultures with the immune serums.

Two of the five patients with lobar pneumonia containing Type 4 pneumococcus died. Whether cocci of another type were also present remains an open question, since no necropsy was permitted. One of the children who recovered had Type 4 pneumococcus in the pleural fluid as well as in the sputum.

While the mortality of the lobar pneumonia patients in this series due to pneumococci of Type 4 was two out of five, or 40 per cent., in

the cases due to Type 1 it was two out of three, or 66⅔ per cent. One of the two children from whom Type 2 pneumococcus was isolated had *Bacillus influenzae* in the sputum at the same time; both recovered. We realize that the number of our cases of lobar pneumonia is very small, and that the bacteriologic results are to be considered as suggestive rather than conclusive.

Two patients with lobar pneumonia did not have any pneumococci in their sputum. But since both recovered the correctness of the clinical diagnosis must be open to question. The sputum from one of these children yielded a growth of streptococci on three separate tests, and one strain proved rather puzzling. Its morphology was that of a pneumococcus, quite different from the other two strains, but it did not ferment inulin and proved insoluble in bile and in optochin. It apparently agglutinated immune serum of pneumococcus Type 1 and Type 2 equally well, the control remaining smooth.[3] The other two strains of streptococcus isolated from the sputum of this child proved to be very virulent for rabbits and dogs. The last case of the series gave a growth of *Staphylococcus aureus* and *Bacillus influenzae* from the sputum and of *Staphyloccus aureus* alone from the pleural pus. Since the child was discharged in an improved condition, there must be a doubt as to whether the pulmonary lesion was a true fibrinous pneumonia, as there is both clinical and experimental proof that bronchopneumonia, as well as lobar pneumonia, may be accompanied by empyema. Again the pneumococcus present in the lung may not have been present in the sputum, though this would seem less probable in the light of the presence of *B. influenzae* whose habitat is the smaller bronchi and so is often missed when only mouth secretions are planted, without successful attempts at cough and expectoration.

Summing up our eleven cases of lobar pneumonia, we find pneumococci of Type 1 present three times, always with Type 4; Type 2 twice; Type 4 alone four times; streptococcus once, and *Staphylococcus aureus* once. The four fatal cases all contained Type 4, and two had Type 1 as well. Four children had pus in the pleural cavity and of these, two died (Type 1) one recovered (Type 4,) and one (*Staphyloccus aureus*) improved.

Blood cultures in these eleven cases of lobar pneumonia were positive in only one case. Type 1 pneumococcus was found, and the baby died. This extremely low percentage of positive blood cultures is to be atributed to the fact that repeated cultures were not taken because of lack of time. The point as to whether a positive blood culture has a bad prognostic significance, as in adults, cannot be illuminated with these results.

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3. This strain was submitted to Dr. Avery at the Rockefeller Hospital, who very kindly made the optochin test and pronounced the organism a streptococcus.

BRONCHOPNEUMONIA

Thirty-six cases of bronchopneumonia were studied, four of the children were suffering from tuberculosis as well. There were fourteen recoveries and eighteen deaths in the series, while one child left the hospital in an improved condition, and three were unimproved. The youngest infant, 25 days old, was admitted for tetanus neonatorum, the pneumonia contributing to the fatal outcome. The age and outcome of the bronchopneumonia cases is shown in the following tabulation, while the bacteria isolated from them are indicated in Table 1.

BRONCHOPNEUMONIA

CURED		UNIMPROVED	
Age	No.	Age	No.
2 yr.	1	2 yr.	1
21 mo.	1	9 mo.	1
19 mo.	1	5 mo.	1
18 mo.	1	DIED	
16 mo.	1	19 mo.	1
14 mo.	1	15 mo.	1
13 mo.	3	14 mo.	1
12 mo.	1	13 mo.	1
9 mo.	2	11 mo.	2
7 mo.	1	9 mo.	5
6 mo.	1	5 mo.	1
		4 mo.	2
IMPROVED		3 mo.	1
4½ yr.	1	2½ mo.	1
		5 wk.	1
		25 days	1

Pneumococci of Type 1 were present in only three cases of bronchopneumonia, and all three patients died.

Type 2 pneumococci occurred in four children with two fatal results, one of which was complicated by tuberculosis. One of the two babies of this group who recovered had *B. influenzae* in his sputum; together with the pneumococcus, and the other had streptococci in addition to pneumococci.

Pneumococci belonging to Type 4 were present in twenty-one of the thirty-six cases of bronchopneumonia, or in 60 per cent. In twenty cases the cocci were isolated from the sputum, in two from the pleural fluid as well, and in one instance from the blood, cerebrospinal fluid, and sputum. Nine of these twenty-one infants died, nine recovered, one improved, and two were discharged unimproved. The high mortality rate of 43 per cent. is directly opposed to the mortality caused by Type 4 pneumococcus in the lobar pneumonia of adults, which is about 10 per cent. The low resistance of infants to infection in general is undoubtedly a factor in explaining the large percentage of pneumonias in infancy caused by the group of pneumococci ordinarily present in the mouth and also in explaining the high death rate.

In eighteen cases pneumococci of Type 4 were found in pure culture in the peritoneal exudate and blood of the inoculated mouse, while twice *B. influenzae* and once *Staphylococcus aureus* came through the circulation of the animals together with the pneumococci.

Most interesting is the fact that in this series of fifty children with pneumonia, only one developed a purulent leptomeningitis, and in this case pneumococci belonging to Type 4 were found in the sputum, blood, and cerebrospinal fluid during life, and in the blood and meningeal pus at necropsy.[4] The pulmonary lesion was very limited and not severe; had it been more marked the general infection might not have occurred. This case also serves to emphasize the fact that in the bronchopneumonia cases in our series there was no discrepancy in the bacterial findings before and after death; that is, the cultures of the sputum and pleural fluids were identical with those made from the lungs at necropsy.

Streptococci were present in three cases of bronchopneumonia, once with a pneumococcus of Type 2. All of these children recovered, a fact which is to be noted.

Staphyloccus aureus was found in the sputum of six infants suffering from bronchopneumonia, of whom two recovered, one improved and three died. Two of the fatal cases were due to *Staphylococcus aureus* alone, while in the third a Type 1 pneumonococcus was associated with it. Type 4 pneumococcus was found with the staphylococcus in two children, of whom one was cured and one improved. The higher mortality rate of the staphylococcus over the streptococcus pneumonias is striking.

B. influenzae appeared in the sputum in six cases of bronchopneumonia, three times in pure culture, with fatal results. It was associated with a Type 4 pneumococcus in two other patients, one of whom died, and with Type 2 pneumococcus in a child who got well. We wish to emphasize the fact that *B. influenzae* in pure culture always causes a bronchopneumonia, never a lobar pneumonia. When present with the pneumococcus in cases of lobar pneumonia it apparently does not modify the pulmonary lesion.

BRONCHITIS

Two cases were studied, one showing a Type 4 pneumococcus and one the streptococcus. Both patients recovered.

POSTPNEUMONIC EMPYEMA

A patient with empyema was admitted to the hospital after the antecedent pneumonia had run its course. Type 4 pneumococcus was

4. During the last few weeks a second case of leptomeningitis came to necropsy, and again Type 4 pneumococcus was isolated from the purulent exudate.

found in the sputum and *Staphylococcus aureus* in the pleural pus. The child improved and the nature of the original lesion remains obscure.

In four additional cases diagnosed as bronchopneumonia the sputum injected into white mice caused no illness in the animals, and no bacteria were found in the peritoneal fluid and blood when the mice were killed, twenty-four hours after inoculation. It is possible that only saliva and not lung exudate was injected, although the child made the usual attempts to cough. These cases serve to emphasize the disadvantage under which work of this kind suffers because of the dangers attendant on lung puncture in young children and the impossibility of obtaining material by that method. A parallel series of specimens of sputum and lung puncture material should be studied.

CONTROLS

Three controls were made with sputum from children who had no lesion in the respiratory tract, but who suffered from pyloric stenosis, rachitis, and malnutrition respectively. No one of the three resulted in positive cultures from the mice injected with a specimen of sputum; that is, the sputum of these three infants contained no bacteria which were pathogenic for white mice.

DISCUSSION

It will be seen that the findings in this series of pneumonias in young children are quite different from those reported by Dochez[2] and his associates in adult patients with lobar pneumonia. In infants bronchopneumonia is a more frequent disease than is lobar pneumonia, and in our series there were twenty-five infants under the age of one year, of whom 16 per cent. had lobar pneumonia and 80 per cent. had bronchopneumonia.

While in adult lobar pneumonias Type 4 pneumococcus is found in only from 20 to 25 per cent. of the cases, with a death rate of about 10 or 13 per cent., in infantile lobar pneumonia it was found in pure culture in 36 per cent. of the cases, though it was present in 63 per cent., with a death rate of 57 per cent. In bronchopneumonia cases, on the other hand, Type 4 pneumococcus occurred in pure culture in 50 per cent., though it was present in 60 per cent., with a mortality of 44 per cent. All the fatalities, strange to say, occurred among the cases in which this coccus was present alone. The three children in whose sputum other organisms were found did not die.

Type 2 pneumococcus was found in two patients, or 18 per cent. of the lobar pneumonia cases. Both children recovered, though one had *B. influenzae* in the sputum as well as the pneumococcus. In the babies with bronchopneumonia, Type 2 pneumococci were found in four, or

TABLE 2.—Incidence of Types 1, 2 and 4 Pneumococcus in Fifty Cases

Disease	In Pure Culture			With Type 4			With Staphylococcus Aureus			With B. Influenza			With Streptococcus		Number of Cases	Mortality, per Cent.	Average Mortality, Each Type, per Cent.
	Cured	Died	Unimproved	Cured	Died	Unimproved	Cured	Died	Improved	Cured	Died	Unimproved	Cured	Died			
Type 1:																	
Lobar pneumonia	0	0	0	1	2	0	0	0	0	0	0	..	0	0	3	66	83, Type 1
Bronchopneumonia	0	2	0	0	0	0	0	1	0	0	0	..	0	0	3	100	
Type 2:																	
Lobar pneumonia	1	0	0	0	0	0	0	0	0	1	0	0	0	0	2	0	33, Type 2
Bronchopneumonia	0	2	0	0	0	0	0	0	0	1	0	..	1	0	4	50	
Type 4:																	
Lobar pneumonia	2	2	0	1	2	0	0	0	0	0	0	..	0	0	7	55	40, Type 4
Bronchopneumonia	7	8	3	0	0	0	1	0	0	1	0	1	0	0	21	38	
Bronchitis	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Postpneumonic empyema	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	

11 per cent.; twice in pure culture, and twice with other organisms. The mortality rate it caused was nil in the lobar cases and 50 per cent. in the bronchopneumonias.

Type 1 pneumococcus occurred in three cases of lobar pneumonia, or 27 per cent., but never in pure culture; in all these cases Type 2 pneumococcus was also present. It caused a death rate of 66 per cent. In bronchopneumonia cases Type 1 pneumococcus was present in only three babies, all of whom died. Table 2 shows these figures, and it will be seen that Type 4 was present in thirty out of a total of fifty cases, or 60 per cent., with a mortality of 40 per cent., against a mortality of 33 per cent. caused by Type 2, and 83 per cent. caused by Type 1.

It seems fair to reason, then, that pneumococci of Types 1 and 2 are more likely to cause a lobar pneumonia in children, while Type 4 is more liable to produce a bronchopneumonia, though with a highly fatal course. Two facts are brought out by the study of this series of cases: (1) that the type of pneumococcus ordinarily present in the human mouth was the cause of 60 per cent. of all pneumonias in a series of fifty cases in young children, and (2) that the most frequent type of pulmonary lesion it produced was a bronchopneumonia, with a mortality of 43 per cent.

The fact that in children so many cases of pneumonia running a severe and even fatal course are due to Type 4 pneumococci cannot be without significance in the epidemiology of the disease. While the pneumococci ordinarily present in human mouths cause only 25 per cent. of lobar pneumonia cases in adults, they cause 60 per cent. of all pneumonias in children, thus serving to maintain the virulence of this type of coccus. In infants and young children Type 4 pneumococci cannot be looked on as innocuous.

Only two of eleven cases of lobar pneumonia failed to show the presence of pneumococci in the sputum, and since both of these children recovered, the correctness of the clinical diagnosis remains unproved. Of the thirty-six cases of bronchopneumonia, on the other hand, eight did not have any type of pneumococcus in the sputum.

In this series pneumonias due to the streptococcus ran a benign course, while *Staphylococcus aureus* caused a mortality which was higher than that due to Type 4 pneumococcus. *B. influenzae,* when present alone, proved fatal in three cases. This may be explained by the fact that only virulent strains of *B. influenzae* are capable of producing pulmonary consolidation, while the strains ordinarily present in the mouth and bronchi together with other organisms are, as a rule, of very low virulence.

SUMMARY

In this series of fifty cases of pneumonia in young children, the comparative frequency (60 per cent.) of Type 4 pneumococcus is noticeable, as is also the high mortality (40 per cent.) rate it caused.

Pneumococci of Types 1 and 2 were present in a higher percentage of lobar pneumonias than of bronchopneumonias; the mortality rate of the cases in which Type 1 was found reached 83 per cent., and Type 2 was fatal in 33 per cent. of the cases in which it occurred. All these figures are much higher than in lobar pneumonia cases in adults, and the greater mortality of Type 1 over Type 2 is also to be noted.

OBSERVATIONS ON THE INTRADERMAL AND REPEATED INTRADERMAL INJECTION OF DIPHTHERIA TOXIN WITH REFERENCE TO THE SCHICK TEST*

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The knowledge of the effect of subcutaneous and, inadvertently, intradermal injection of diphtheria toxin on the cutaneous tissue, is as old as the knowledge of diphtheria antitoxin. It was necessarily one of the first observations made during the process of immunization and of testing out the strength of diphtheria antitoxin. A great deal of the knowledge accumulated at that time has a distinct bearing on the interpretation of the phenomena now seen in the cutaneous reaction known as the Schick test.

Soon after the appearance of the reports concerning the clinical value of the intradermal diphtheria toxin test, I became interested in studying the character of the reaction and its behavior under the influence of repeated injections. My interest was held because of the occurrence of happenings analogous to those encountered with repeated injections of horse serum and cowpox vaccine, which had to be explained on entirely different grounds, and also because of the fact, observed so many times in my series of primary injections, that reactions are frequently delayed beyond the usual twenty-four to forty-eight-hour period, to as late as three or four days. Finally, the chief object of my study was to determine if possible, by means of this simple reaction, whether any degree of active immunity could be induced by these infinitesimally small doses of diphtheria toxin.

The enormous change in the biochemic state of the body that is induced by minute amounts of horse serum, egg white, etc., and the well-known peculiar animal racial differences of reaction to injected substances of various kinds seemed to warrant one in devoting some time to this study, even though it had been quite generally admitted that the injection of such small doses of toxin as are represented in 0.1 c.c. of the solution used for the Schick test could have no effect in the production of immunity.

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Toxin Employed and Method of Injection: The two lots of diphtheria toxin use were kindly furnished by Parke, Davis & Co. of Detroit. The L + dose of Lot 1 is 0.18 c.c., of Lot 2, 0.18 c.c. The minimum lethal dose of Lot 2 was estimated to be 0.0015 c.c. Both lots came from the same original supply. The former lot was not so constantly kept on ice as the latter. Except when otherwise specified, Lot 1 may be understood to have been used. The usual fine, sharp needle method of intradermal injection with an all-glass finely graduated tuberculin syringe was used in making the injections, 0.1 c.c. being carefully injected intracutaneously just beneath the epidermis.

Part I

Of eighty-one persons taken at random, ages varying from 2 days to adult life, in whom careful daily observations and measurements were made, fifty reacted positively and thirty-one negatively. These injections were made during the months of November, December, January, February, March and April, 1914 and 1916.

Of the fifty positively reacting cases, the first evidence of a definite reaction was observed on the first day in twenty-one cases; on the second day in thirteen cases; on the third day in eight cases, and on the fourth day in eight cases.

Of these fifty cases, the height of the reaction (the maximum) was reached on the first day in eight cases; on the second day in ten cases; on the third day in twenty cases; on the fourth day in eleven cases, and on the fifth day in one case.

Of the eight reactions showing themselves first on the fourth day, all faded away very quickly, within forty-eight hours of their appearance. Of the twenty-one first-day reactions, twenty faded away very slowly, many showing distinct discoloration beyond the seventh day; and one, Case 56, showing a faint reaction, faded away quickly; but a note made five days after the injection records a "stain"; it was accordingly regarded as a positive case. Reactions appearing on the second and third day, like those appearing on the first day, also disappeared slowly. These cases will be referred to again under the caption "Successive Injections."

The age incidence of reaction of the eighty-one patients is as follows:

	Positive	Negative	Total	Per Cent.
Under 5 months	4	13	17	23
5 to 12 months	5	1	6	83
1 to 5 years	21	3	24	87
6 to 12 years	13	12	25	52
Adults	7	2	9	77
Total	50	31	81	62

Observations on the Effect of Varying Strengths of Diphtheria Toxin.—In a susceptible person distinct, measurable and typical reactions were obtained with toxin dilutions as high as 1 to 50,000. One-tenth c.c. of this solution represents two millionths of a gram, or two thousandths of a milligram of toxin. By reference to Figures 1, 2, 3, 4, 5 and 6, forearm D. O. W., the progress of the reactions of the six different dilutions may be seen. The amount of toxin contained in 0.1 c.c. of these solutions is as follows:

No.	Dilution	Dose, C.c.	Toxin, Gm.
1	1 to 50,000	0.1	0.000002
2	1 to 40,000	0.1	0.0000025
3	1 to 30,000	0.1	0.0000033
4	1 to 20,000	0.1	0.000005
5	1 to 10,000	0.1	0.00001
6	1 to 5,000	0.1	0.00002

The exact measurements and other daily recorded phenomena of the reactions will be found in Table 1. It will be observed that, as one should expect, increasing concentrations of the solutions, namely, the greater the quantity of the toxin, the more vigorous the action of the toxin on the unprotected cutaneous cells, and vice versa, the less the reaction of the body against the toxin. This distinctive effect of the toxin on the upper skin structures can go on up to the point of producing a large blister, Figures 7, 8 and 9, without producing any appreciable harm to the individual aside from the local discomfort which comes in these cases. A series of thirteen tests was made, 0.1 c.c. toxin (L + dose 0.18 c.c.) of a dilution of 1 to 1,000, that is, 0.1 mg. of toxin being used. The reactions are recorded in Table 2. Large vesicle formations (blisters) were observed in five of these cases, namely, 4, 6, 7, 8 and 13.

So much has been written concerning the character of a typical reaction that I shall refer to but a few points here: (1) the interpretation of a two-zone reaction; (2) the character of the periphery of the lesion; (3) the occurrence of scaling or desquamation; (4) the size of the reaction as influenced by the strength of the toxin; and (5) edema.

1. The Two-Zone Reaction: The statement is not infrequently made that a lesion with a dark center surrounded by a lighter pink areola, such as one so commonly sees in second intradermal injections of horse serum, should be looked on with suspicion as an indication of a pseudo or anaphylactic reaction. While doubtless a pseudo or protein reaction may occur with diluted diphtheria toxin, what I have termed a two-zone lesion does very frequently occur as a result of the action of the toxin itself. It is only a matter of either concentration, as is shown in Figures 1 to 6, or of individual tolerance, as is seen with the

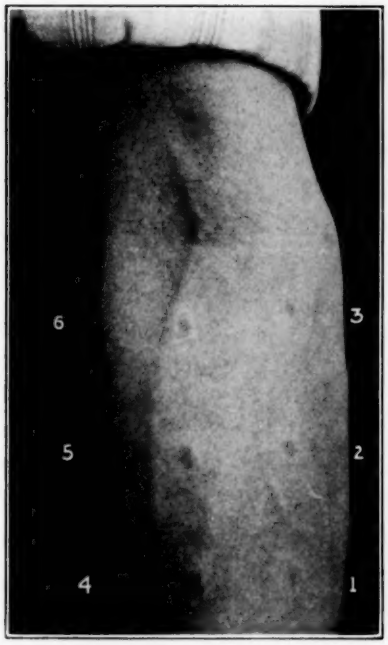

Fig. 1.—Twelve hours after injection. This and the five succeeding illustrations show the progress of the reactions of the six different dilutions: 1, 1 to 50,000 dilution toxin; 2, 1 to 40,000; 3, 1 to 30,000; 4, 1 to 20,000; 5, 1 to 10,000; 6, 1 to 5,000. A reading glass will aid greatly in bringing out the detail of the lesions.

Fig. 2.—Twenty-four hours after injection. Note the slight general swelling. The vein is less visible.

Fig. 3.—Second day. General swelling more marked.

Fig. 4.—Third day. Vein cannot be seen.

Fig. 5.—Sixth day; 5 and 6 (see numbers as given in Figure 1) show wrinkling.

Fig. 6.—Eighth day; 5 and 6 (see numbers as given in Figure 1) desquamating.

Fig. 7.—Lesion following the intradermal injection of 0.1 c.c. toxin diluted 1 to 1,000.

Fig. 8.—Lesion following the intradermal injection of 0.1 c.c. toxin (L + dose 0.18 c.c.) diluted 1 to 1,000. This and figure 7 illustrate the same case, different views. There are three well-defined zones—the vesicle, the anemic area surrounding it, and the pink areola.

Fig. 9.—Lesion following the intradermal injection of 0.1 c.c. toxin (L + dose 0.18 c.c.) diluted 1 to 1,000.

TABLE 1.—Reactions Following Varying Strengths of Diphtheria Toxin Administered Intradermally

Date	Time After Injection	Site Number	Description of Reaction
4/12/16	12 hours	1	1 to 50,000. Faint hyperemia 13 × 17,* diffuse, flat
		2	1 to 40,000. Definite hyperemia 17 × 21, definite border, flat
		3	1 to 30,000. Definite hyperemia 15 × 22, pale red, definite border
		4	1 to 20,000. Marked hyperemia 17 × 18, light red, slightly elevated in center
		5	1 to 10,000. Marked hyperemia 20 × 25, red, definite border, slight elevation, pain on pressure
		6	1 to 5,000. Marked hyperemia 22 × 25, center deeper red, 5 × 7, elevated
4/13/16	24 hours	1	15 × 20, diffuse border, flat, pink.
		2	17 × 25, more definite border, flat; more hyperemic than 1
		3	22 × 27, more definite border, slightly more hyperemic than 2
		4	20 × 27, definite border, center slightly elevated, deeper pink, slight tenderness
		5	27 × 35, definite border, elevated slightly, not as much as 4, deeper pink, no tenderness
		6	28 × 35, border indefinite, same color as 5, darker pink zone at center, 5 × 5, slightly tender; slight edema. See Figure 2
4/14/16	2d day	1	10 × 10, pink tint, distinctly fading, flat, margin more definite
		2	15 × 15, pink tint, distinctly fading, flat, margin more definite
		3	15 × 15, pink tint, distinctly fading, flat, margin more definite
		4	15 × 15, pink tint, distinctly fading, deeper pink than 1, 2, 3, flat. Slight wrinkling
		5	20 × 23, deeper pink than 4, definite border, flat, pain on pressure, slight wrinkling
		6	20 × 30, slightly deeper pink than 5, definite border, flat, pain on pressure, slight wrinkling. The whole arm is slightly swollen and there is a slight pinkish hyperemic flush surrounding all the areas measuring 120 × 75
4/15/16	3d day	1	10 × 10, yellowish brown stain, not hyperemic
		2	10 × 15, fading, dull pink, slightly hyperemic, margin more diffuse
		3	10 × 15, fading but brighter than 2, hyperemic, flat, margin more diffuse
		4	15 × 15, fading but brighter than 3, hyperemic, flat, very slight wrinkling
		5	20 × 23, bright red, darker than previous day, hyperemic, flat, no soreness
		6	18 × 30, same as 5, flat. The general hyperemia described for 2d day has gone and the general swelling or edema of the forearm is distinctly less, but still noticeable, the veins are still obliterated
4/16/16	4th day	1	Almost gone, stain, which cannot be measured. The whole diffuse suggestion of discoloration was about 15 × 15
		2	10 × 15, just visible, brownish pink, no definite outline
		3	Seems smaller than 2, cannot measure, fading
		4	Fading, very finely wrinkled, about 15 × 15
		5	20 × 23, still dark pink, faded since 3d day, more dry on surface, wrinkled a little
		6	15 × 25, a little more marked than 5, no scaling, no marked wrinkling, general swelling less, veins still invisible

* Measurements are given in millimeters.

TABLE 1.—Reactions Following Varying Strengths of Diphtheria Toxin Administered Intradermally—(*Continued*)

Date	Time After Injection	Site Number	Description of Reaction
4/17/16	5th day	..	All fading markedly
		1	Stain just seen
		2	10 × 15, fainter than 4th day
		3	10 × 10, fading, very diffuse border
		4	Same, a little more wrinkled
		5	Nearly the same, border less defined, wrinkled a little more
		6	Same, 15 × 25, deeper red than others, otherwise same as 5
4/18/16	6th day	..	All very much more faded
		1	2, 3 and 4 cannot be measured
		5	15 × 20
		6	15 × 25
		4	5 and 6 more wrinkled, no scaling yet
4/19/16	7th day	..	All fading much more
		1	Almost invisible
		5	and 6 scaling in large flakes
4/21/16	8th day	1	and 2, no scaling
		3	Faint
		4	5 and 6 marked

standard Schick reaction (0.1 c.c. = 0.5 minimum lethal dose of toxin). This type of reaction is plainly seen in Figure 10. There is distinct edema in the center, and little or none at the periphery; necessarily there will be a difference in the color at these two places. A perfectly uniform color is probably more commonly seen than this two-zone reaction, however; even in some reactions that seem to be faint, careful observation will show not infrequently a darker central area surrounded by a lighter areola.

2. The Margin of the Lesion: The statement is sometimes made that the margin of the lesion must be well defined. This, too, depends largely on the strength of the solution and the susceptibility of the individual. In many of the reactions cited in this report, as well as in the series shown in Figures 1 to 6 and in Table 2, the statement, "diffuse border, the lesion cannot be measured, etc.," will be encountered frequently. We have had previous proof of a positive reaction in some of these individuals, who now react less markedly because of a certain degree of immunity. This diffuse margin is well shown at sites

TABLE 2.—DIPHTHERIA TOXIN 1 TO 1,000 (L + D 0.18 C.C.) 0.1 C.C. INTRADERMALLY, SEPT. 22, 1915

Case No.	Name	12 Hours	18 Hours	24 Hours	36 Hours	5 Days
1	Mr. B.*	7 × 9,† pale pink	10 × 10, red, elevated, definite border	15 × 15, faint pink, raised, margin red, center 2 × 3	.....	8 × 8, red area, no induration
2	Mr. H.	20 × 20, marked reaction, marked elevation, edema	20 × 25, same as at 12 hours	30 × 35, pale pink area, red center 15 × 15, border indefinite	20 × 20, pink fading	Fading
3	Mr. S. B.	7 × 8, very pale pink, no elevation	10 × 12, red, definite border, elevated	12 × 12, same as at 18 hours	.....	Fading
4	Miss D.	17 × 22, red, elevated, definite border	23 × 25, same tint, border fading	35 × 35, elevated, indurated, border definite	25 × 25, red center, pink area	
5	Miss R.	11 × 12, deep red, definite border, slight elevation	10 × 10, pale pink border indefinite, slight elevation	18 × 28, deep red center 8 × 8, pink area, border definite, all elevated	10 × 10 vesicle area red and edematous	10 × 10, vesicle dry, area about it 5 mm. wide. Total area 15 × 15
6	Miss S.	17 × 22, deep red, marked elevation, border definite	23 × 35, same as at 12 hours	23 × 35, same as at 18 hours	Arm bandaged, definite blister formed	Arm bandaged, definite, blister formed
7	Mr. B.	10 × 13, pale pink, diffuse border	17 × 20, pale pink, definite border	.....	20 × 25, pink, fading	Blister 12 × 15, area about it 4 mm. wide, total area 15 × 19
8	Miss F.	18 × 22.....	.....	.....	50 × 70, red center, 20 × 22, area red	Vesicle said to have formed, not seen
9	Mr. O.	20 × 20, center elevated, hyperemia fades at border	40 × 30, pink with bright red center	40 × 30, same as at 18 hours	55 × 80, red, elevated center marked, border pink	10 × 10, pigmented rough area, desquamating
10	Mr. E.	22 × 30, bright red, marked elevation, border definite	28 × 30, same as at 12 hours			
11	Mr. G.	10 × 20, pink, flat, fading margin	.....	.....	30 × 40, slight edema, no vesicle	
12	Mr. Er.	10 × 15, pale pink, flat	14 × 15, pink, slightly elevated, border definite	14 × 15, same, but border less distinct	10 × 20, pink fading, no elevation	Negative
13	Miss S.	18 × 25, deep red, elevated, border definite	20 × 25, same as at 12 hours	30 × 35, bright red, margin raised	30 × 35, pink fading, no edema	Blister 20 × 30, 4 mm. high, area 45 × 60, white anemic band around vesicle 5 mm. wide. See figures 7 and 8

* Patient had 1,000 units of antitoxin subcutaneously.
† Measurements are given in millimeters.

1 and 2, Figure 2. A definite impression of a typical reaction is here gained, but one could not definitely measure the lesion. It is very difficult to get a good photograph of a faint pink lesion. Many photographs of Schick tests show a measureable lesion with a definite border, when in fact beyond the area which seems fairly sharply defined is a gradually diminishing zone which fades almost imperceptibly into the color of the skin.

3. The Occurrence of Scaling: The typical lesion following the injection of 0.1 c.c. of Schick solution into a distinctly susceptible person almost, although not invariably, finishes up with characteristic

Fig. 10.—Madelain B., photograph taken March 28, 1916, eight days after the first intradermal injection: 1, first intradermal injection of 0.1 c.c., 1 to 20,000 dilution, on March 20; 2, second intradermal injection of 0.1 c.c., dilution 1 to 10,000, March 21; 3, third intradermal injection of 0.1 c.c., dilution 1 to 10,000, March 25. Nos. 1 and 2 are desquamating. Entire lesion elevated 1 mm. above surface, and has a leathery, thickened feeling. Total area at 3 is 18 × 25 mm., pink, central portion dark pink, slightly elevated, slight edema. The two zones are distinguishable.

scaling or desquamation, Figures 6, 10 and 12. As here shown, the lesion is often elevated well above the level of the skin. In less susceptible persons only a yellowish or brownish yellow stain remains, and this may vanish very quickly. This is well shown in the case recorded in Figure 11. This patient, after a degree of acquired immunity, gave no scaling at the point of the fifth injection. The same result, no scaling, was encountered many times in the series of successive injections.

4. The Size of the Reaction as Influenced by the Strength of the Solution: The average maximum size of lesions produced by different dilutions of the same lot of toxin is given as follows, the measurements being taken from the fifty positive cases in the primary series of eighty-one cases:

Dilutions	No. of Cases	Average Maximum Reaction, Mm.	Amount Toxin, C.c.
1 to 20,000	10	10.9 × 15.1	0.000005
1 to 10,000	34	15.5 × 14.6	0.00001
1 to 1,000	13	27.4 × 34.6	0.0001

The reactions obtained with 1 to 20,000 and 1 to 10,000 solutions are the same, while those with the stronger solutions are very much greater in size.

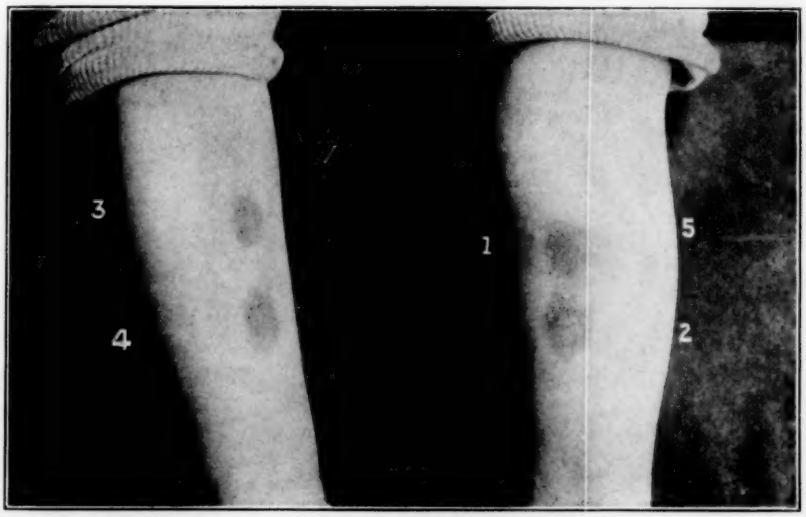

Fig. 11.—Madelain B., received on March 28, 1916, the fourth intradermal injection of 0.1 c.c. of toxin, and on April 11 the fifth injection of the same quantity on the left forearm just to the right of No. 1. The photograph was taken April 13. The age of each lesion on this date was as follows: 1, twenty-nine days; 2, thirty days; 3, nineteen days; 4, sixteen days, and 5, two days. This illustrates the diminishing reaction following successive injections No. 5, while 30 × 35 mm. was only a faint flush; the day following it was a light brown stain. Observe that lesions 1 and 2 are still very noticeable.

The size of the reaction as influenced by the same dilution of different lots of toxin varies according to the strength of the toxin itself. No two lots of toxin are necessarily the same. On request, Parke, Davis & Co. of Detroit have kindly furnished me with the L + dose of five lots of diphtheria toxin taken at random, to which I add that of the lot used in making these tests, as follows: 0.5 c.c., 0.29 c.c., 0.25 c.c., 0.5 c.c., 0.29 c.c., 0.18 c.c. The L + dose of toxin used by Schick was

0.005 c.c.; accordingly, if one uses a standard-sized needle to deliver a definite amount of toxin into the skin, as has been recently advocated by Dr. Koplik, a definitely standardized toxin should be used. Susceptibility to diphtheria toxin, and consequently to diphtheria, can be recognized by very much more dilute solutions of toxin than are usually employed in making the Schick test.

The size of the reaction may be different with the same lot of toxin, the reason for which is hard to explain. For example, Mr. W. was given 0.1 c.c. of a 1 to 10,000 solution of Lot 1 and 0.1 c.c. of Lot 2. The lesion resulting from Lot 1 was very much more vigorous than that resulting from Lot 2, as will be seen in Table 3.

Fig. 12.—Loretta B., photograph taken March 28, 1916, eight days after the first injection, seven days after the second, and three days after the third. The effect of repeated injections is shown. This patient, like the one in Figure 11, continued to react positively after eight injections covering a period of over forty days. The reactions, however, are much modified, more superficial, and fade very much more quickly.

TABLE 3.—Variation of Reaction Due to Difference in Toxins

Toxin Lot	Ten Hours	End of First Day	End of Second Day	End of Third Day
1	+	20 × 20, deep pink, dark center 5 × 5 mm., elevated	10 × 11, deep pink, diffuse border, edema	7 × 8, fading pinkish, can't measure
2	0	15 × 15, fainter, flat	12 × 15, pink, red, flat, border diffuse	9 × 11, deep pink, flat, diffuse

Lot 1 happened to be an old solution, having stood many weeks. We would naturally expect this solution to deteriorate and give a weaker reaction than was obtained with the fresh solution, Lot 2. The solution was perfectly clear, however, and free from visible growth.

5. Edema: The intensity of the reaction, which seems to be indicated by the degree of redness and edema as well as by the size of the lesion, also depends on the strength of solution employed and the susceptibility of the person. In other words, there is no person the intensity of whose lesion cannot be varied at will by the choice of the strength of the solution injected. On the other hand, only those who possess little or no immunity react to the standard Schick solution with marked edema and induration. Such edema, for example, as can easily be seen and felt. Lesser degrees of edema, determined by pressing the lesion with the thin edge of the measuring rule or of the steel tape, are very commonly seen.

Reactions in Infants.—Intradermal tests were made on twenty-three infants, ages varying from 2 days to 10 months (ten positive, thirteen negative, or 56.5 per cent. negative). Negative reactions were encountered very frequently in infants under 5 months. No satisfactory explanation has been given for this immunity. It seems to have been a common clinical observation that young infants are seldom infected with diphtheria. Some authors go so far as to state that diphtheria never attacks an infant in the first half year of life, and believe this is due to a complete immunity. While my short series of cases seems to show that quite a large percentage of infants during this period of life are immune, there is still a large percentage who are not immune. This is rather in accord with the observations of Welch and Schamberg, who state that it has fallen to their "lot to see a large number of infants perish from this scourge (diphtheria) and many of them were under the age of 6 months." In their collection of 9,011 cases, 299, or 33 + per cent. were in infants under 1 year. Some observers, notably Schick, found only 7 per cent. of positively reacting cases in infants under 6 months. Similar results were obtained by Kassowitz and Gröer,[1] who report 10 to 20 per cent. positive. On the other hand, Kleinschmidt[2] found no antitoxin in sixteen out of eighteen infants examined.

It is sometimes very difficult to determine reactions of moderate degree in the newly born, because of erythema neonatorum, and particularly in some cases of icterus neonatorum, associated with erythema

1. Kassowitz and Gröer: Jahrb. f. Kinderh., 1913, lxxviii, 609.
2. Kleinschmidt: Jahrb. f. Kinderh., 1913, lxxviii, 442.

neonatorum. A very good light and a very careful observation is necessary, while in infants beyond the first two or three weeks of life the lesion is as easy to see as it is in a blond.

Family Reactions.—Park[3] and his co-workers have called attention to the interesting point of family reactions; that is, if it is found that one member of a family of children reacts negatively or positively to a Schick test, all the rest of the children react in the same way. This observation has been confirmed by others. An early observation bearing on this point is that of Theobald Smith,[4] who in 1907 showed that conferred diphtheria immunity was transmitted to the offspring of guinea-pigs. It was further shown that this immunity remained active only over a period of thirty days, after which it gradually decreased until six months, when the offspring were no longer immune. This suggested to me the advisability of testing the mother and infant. The data obtained in this investigation are shown in Table 4.

TABLE 4.—Results of Intradermal Test Applied to Mother and Child

Number	Mother		Reaction in Infant	Age of Infant, Days
	Name	Reaction, Mm.		
1	West	15 × 15	Negative	10
2	Gray	20 × 21	Negative	9
3	Haynes	++20 × 25	Positive, 10 × 15	3
4	Prum	++20 × 25	Negative	2
5	Sweet	0	0	10
6	Bibbins	++30 × 30	0	3
7	McClure	++15 × 20	Positive +	4
8	Calhoun	++25 × 25	Positive +	6
9	Armstrong	++20 × 25	Positive ++	4

Table 4 shows that the mother and child were both positive in four instances, both negative in one instance, and mother positive and child negative in four instances. From these data it will be seen that while mother and child usually react in the same way, the infant may frequently give a negative reaction and the mother a positive. Kassowitz and Gröer believe the antitoxin is derived from the mother. The observations made above would lead one to believe that there are probably factors other than transmitted immunity entering into the negative reaction of the new born.

3. Park, Zingher and Serota: Arch. Pediat., 1914, p. 484.
4. Smith, Theobald: Jour. Med. Research, 1907, xi, 359.

Influence of Time of Year on the Reaction.—It is a well-known clinical fact that diphtheria is more prevalent during certain seasons of the year. The U. S. Mortality Report for 1900, for example, records 16,368 deaths from diphtheria. Of these, 13,848 occurred during the cool and cold months, while 2,520, or about 15 per cent., occurred during the warm months, June, July and August. The influence of season on susceptibility of animals to diphtheria is well known, and has been recorded by Brown.[5] The guinea-pigs used in their experiments were more susceptible to diphtheria toxin mixtures in winter than in summer.

A great many toxin Schick reactions have been recorded in the literature, but, unfortunately, the time of year at which these reactions were made is frequently not given. One may infer, however, from the date of publication and from the context the time of year at which the test was made. The cases recorded in Table 5 are, I believe, trustworthy as to season. The figures are only suggestive. It is not at all improbable, however, that it will be found that more negative reactions will be encountered in the warm summer months than in winter.

TABLE 5.—INFLUENCE OF SEASON ON SUSCEPTIBILITY TO DIPHTHERIA AS RECOGNIZED BY THE SCHICK TEST

Age	Summer				Winter				Reporter
	No. Cases	Pos.	Neg.	Per Cent. Pos.	No. Cases	Pos.	Neg.	Per Cent. Pos.	
Under 1 year...	20	6	14	30*	48	16	32	33.3	Moffett and Conrad*
One year.....	27	9	18	33.3*	36	20	16	55.5	Moody†
One to 5 years.	..	..	..	....	24	21	3	87.5	Author
Totals.....	47	15	32	31	131	66	65	58	

* Moffett and Conrad: Jour. Am. Med. Assn., lxv, 1010.
† Moody: Jour. Am. Med. Assn., lxiv, 1206.

PART II

SUCCESSIVE INJECTION SERIES

Of thirty-four positive cases in which successive intradermal injections of toxin were given (Table 6) at intervals of five, twelve and seven days, respectively, the time of the reaction was unchanged in nine cases, hastened in twenty cases, delayed in no instance, and completely suppressed in five instances. The character of the reaction was unchanged in five cases, diminished in twenty-four cases, and suppressed in five cases.

5. Brown: Jour. Med. Research, 1912-1913, xxii, 447.

TABLE 6.—Successive Intradermal Injections in Positive Cases

Case Number	1st Injection, Dilution 1 to 10,000		2d Injection, 5 Days after 1st, Dilution 1 to 10,000		3d Injection, 17 Days after 1st, Dilution 1 to 5,000		4th Injection, 29 Days after 1st, Dilution 1 to 10,000		5th Injection, 36 Days after 1st, Dilution 1 to 20,000		Influence of Successive Injections	
	Maximum Reaction, Mm.†	Day 1st Reaction	Maximum Reaction, Mm.	Day 1st Reaction	Maximum Reaction, Mm.	Day 1st Reaction	Maximum Reaction, Mm.	Day 1st Reaction	Maximum Reaction, Mm.	Day 1st Reaction	On Time of Reaction	On Character of Reaction, Size, Intensity, etc.
1*	+	2	+	2	.....	...	.....	...	.....	...	Unchanged	Unchanged
2*	7 × 7	3	8 × 10	1	8 × 8	2	10 × 17	1	6 × 7	1	Hastened	Diminished
3*	15 × 22	3	4 × 5	1	10 × 17	1	.....	...	.....	...	Hastened	Diminished
7*	10 × 15^3	1	13 × 18^2	1	12 × 15^2	1	10 × 15	2	8 × 10	1	Unchanged	Diminished
9*	15 × 17	4	15 × 18^4	3	6 × 8	2	±	1	7 × 8	1	Hastened	Diminished
11*	8 × 10	4	±	2	.....	...	.....	...	.....	..	Hastened	Diminished
16	10 × 20	3	3 × 7	1	.....	...	.....	...	.....	...	Hastened	Diminished
17	12 × 12^3	2	20 × 20^3	1	.....	...	.....	..	8 × 10	1	Hastened	Diminished
18	15 × 15^5	2	7 × 10	1	9 × 6^2	1	5 × 5	1	7 × 10	1	Hastened	Diminished
19	10 × 10^3	1	8 × 10	1	12 × 17^4	1	6 × 8	1	10 × 12^2	1	Unchanged	Diminished
20	7 × 10^3	3	0	0	.....	...	.....	...	.....	...	Suppressed	Suppressed
21	8 × 10	2	10 × 14^4	2	7 × 7	1	6 × 9	1	12 × 12	1	Hastened	Diminished
22	10 × 13	1	5 × 3	1	.....	...	5 × 6	1	5 × 8	1	Unchanged	Diminished
23	8 × 8	3	11 × 11^2	1	.....	...	.....	...	8 × 10	1	Hastened	Unchanged

24	10×12	3	15×15	3	.....	...	7×7	1	8×10	1	Hastened	Diminished
25	$\pm$	4	4×4^{1}	1	.....	...	.....	...	.....	..	Hastened	Unchanged
26	15×15	1	5×5^{2}	1	.....	...	10×13	1	12×12	1	Unchanged	Diminished
27	18×20^{4}	2	8×15^{3}	1	8×10^{2}	1	8×12	1	8×10	1	Hastened	Diminished
28	12×15^{4}	2	2×2	1	.....	...	.....	...	.....	...	Hastened	Diminished
29	17×20^{2}	2	+	1	.....	...	.....	...	.....	...	Unchanged	Diminished
30	10×18^{3}	1	10×16^{3}	2?	8×7^{2}	1	.....	...	.....	..	Unchanged	Diminished
32	12×15	3	+	1	.....	...	.....	...	.....	..	Hastened	Diminished
33	8×10	4	+	2	.....	...	.....	...	.....	...	Hastened	Diminished
36	+	1	0	0	.....	...	.....	...	.....	...	Suppressed	Suppressed
39	10×15	4	10×10	3	.....	...	.....	...	.....	...	Hastened	Unchanged
45	12×20^{3}	2	16×20	2	5×7	1	.....	...	.....	...	Hastened	Diminished
46	18×22	2	19×20	2?	16×17	2	.....	...	.....	...	Unchanged	Diminished
52	15×20^{2}	1	8×8^{4}	1	.....	...	.....	...	.....	...	Unchanged	Diminished
53	12×15^{3}	2	10×10^{4}	2?	10×17^{2}	1	8×5	1	8×10	1	Hastened	Diminished
54	3×5^{3}	3	0	0	.....	...	.....	...	.....	...	Suppressed	Suppressed
56	$\pm$	1	0	...	.....	...	.....	...	.....	...	Suppressed	Suppressed
57	5×8	4	$\pm$	2	.....	...	.....	...	.....	...	Hastened	Diminished
59	5×8	4	0	0	.....	...	.....	...	.....	...	Suppressed	Suppressed
61	10×12^{3}	2	10×10	2	10×13	1?	.....	...	.....	...	Hastened	Unchanged

* The patients in Cases 1, 2, 3, 7, 9 and 11 received for the first injection a dilution of 1 to 20,000.
† In the maximum reaction column the exponent indicates the day on which the maximum reaction occurred.

Suppressed Reactions.—The suppressed reactions seem to have been brought about definitely by the repeated injection of toxin. All of these cases gave small but nevertheless distinct primary reactions. In two cases the primary reactions were delayed. The suppression was induced by the first injection of toxin.

The Hastened Reactions.—Of the twenty cases in which the time of the appearance of the reaction was hastened by successive injections of toxin, a primary reaction occurred on the second day in eight cases, on the third day in six cases, on the fourth day in six cases.

Of the eight cases reacting on the second day, the hastening of the time of the reaction was effected by the first injection in four cases, by the second injection in four cases.

Of the six cases reacting on the third day, the hastening of the time of the reaction was effected by the first injection in five cases, by the second injection in one case.

Of the six cases reacting on the fourth day, the hastening of the time of the reaction was effected on the first day in four cases, on the second day in one case.

From this observation it seems that the hastening of the time of the reaction is usually effected by the first injection, that is, a delayed primary reaction case through the influence of the first injection responds more quickly to a second injection after an interval of five days.

While analogous to the phenomena seen after second injections of horse serum, this change in reactivity is not an anaphylactic affair. It is in all probability due to an acquired immunity.

The Diminishing Reactions.—Twenty-four of the positively reacting cases showed a diminution in the size and the intensity of the reaction. This was very noticeable in twelve cases (Cases 3, 9, 11, 16, 22, 28, 29, 30, 32, 33, 45, 52, Table 6). The time of the first appearance of the reaction was hastened in sixteen of these cases, unchanged in eight, but in the latter, seven reacted primarily on the first day. In those cases in which the primary reaction occurred on the fourth day the reaction was so slight after the second injection (which was given five days later) as to be marked "+—" in two (Cases 11, 57, Table 6), and "+" in 1 (Case 33). In other words, it was a question whether there was a reaction at all in two cases, with the benefit of the doubt given to the positive side.

The successive changes which occur in the diminishing group of reactions will be appreciated better by referring to Tables 7 to 11, which give the daily measurements, etc. These tables are self-explanatory.

TABLE 7.—Case 9, Clarence Y., Age 11 Years*

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	0	0	0	15 × 17, red	15 × 17, fading	Fading	Fading
2	11/12/14	1 to 10,000	0	0	±	15 × 18, faint	Fading	Fading	Fading
3	11/24/14	1 to 5,000	+ ?	6 × 8	..	Fading	Fading	Fading	Fading
4	12/ 6/14	1 to 10,000	±	Fading	0	0	0	0	0
5	12/12/14	1 to 10,000	7 × 8	Fading	0	0	0	0	0

* This case illustrates the hastened and diminishing reaction.

TABLE 8.—Case 18, Baby W.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	?	++	++	12 × 12	15 × 15,	Fading	Fading
2	11/12/14	1 to 10,000	7 × 10	+ papule	+	+	Fading	Fading	Fading
3	11/24/14	1 to 5,000	5 × 7, bright red	6 × 9	....	Fading	Fading	Fading	
4	12/ 6/14	1 to 10,000	5 × 5	8 × 8, stain	0	0	0		
5	12/12/14	1 to 20,000	7 × 10	Fading quickly	Stain	—	—		

TABLE 9.—Case 22, Baby R.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	10 × 13	10 × 12, red	8 × 9, fading	Fading	Fading	Fading	Fading
2	11/12/14	1 to 10,000	5 × 3	+	+	Stain	Fading	0	
3	11/24/14	1 to 5,000	5 × 7	8 × 8	....	Left hospital			
4	12/ 6/14	1 to 10,000	5 × 6	5 × 6	0	0	0	Returned to hosp.	
5	12/12/14	1 to 20,000	5 × 8	Fading	0	0	0		

TABLE 10.—CASE 45, GENEVIEVE H.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	0	+	12 × 20	Fading	Fading	Fading	Fading
2	11/12/14	1 to 10,000	....	16 × 20	16 × 20	17 × 20, fading, general rash*	Fading	Fading	Fading
3	11/24/14	1 to 5,000	5 × 7, faint	8 × 8 ?, faint	Left hosp.				

* On Nov. 16, 1914, nine days after the first injection and four days after the second, the patient broke out with a general erythematous eruption, macular in character. This was most noticeable on the right side of the face, where there was a map-like area 7 by 7 cm. There were several large areas on the chest and abdomen 5 by 5 cm. and a few on the arms 2 by 2 cm. The color was deep red. The lips and the lower eyelids were swollen. The cervical glands on the left side were enlarged, but no previous note had been made of their condition prior to injection.

TABLE 11.—CASE 30, ZENA B.

Inj. No.	Date of Injection	Dilution of Toxin	Reaction in Mm.						
			1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day
1	11/ 7/14	1 to 10,000	6 × 13	±	10 × 18	12 × 18	Fading, yellow	Yellow	Fading
2	11/12/14	1 to 10,000	....	8 × 8	+ not measured	10 × 16, fading	Fading	Fading	Fading
3	11/24/14	1 to 5,000	6 × 7	7 × 8, faint	+ not measured	Fading	Fading	Fading	

The question of delayed appearance of primary reactions referred to in the first part of this report seems to be of some significance. In quite a number of the suppressed and diminishing reaction cases the change consequent on repeated injections of toxin to negative or slight reactions is quite noticeable in the late primary cases. From this, one might infer that individuals reacting to a primary injection of diphtheria toxin on the first day have less immunity than those reacting on the third and fourth day. In other words, a delayed reaction means that the individual has a certain amount of immunity, and will, in all probability, be a case which would more readily become immunized by injection of toxin or toxin-antitoxin mixtures.

The Unchanged Reactions.—Those cases in which the character of the reaction was unchanged are four in number (Cases 1, 23, 25 and 61, Table 6). Two of these cases (1 and 25) were of slight reaction, and the patients passed from under observation after the second injection. The other two (23 and 61) were apparently uninfluenced by repeated injections. In Case 23 the patient missed the third and fourth injec-

tions, thus leaving a period of thirty days between injections. This case, however, showed reaction within the first twenty-four hours, while the reaction did not appear until the third day after the first injection.

Negatively Reacting Cases.—Of the patients reacting negatively to successive injections of diphtheria toxin, sixteen remained in the hospital long enough for a second and third injection, given at intervals of five, twelve and fourteen days. Fourteen of these remained negative, while two gave slightly positive reactions after the second injection. These must be considered variants. Case 58 may have been positive after the primary injection, we marked it "— ?," while Case 15, on the other hand, followed the usual distinctly negative course. The reactions were carefully watched over periods of from five to seven days.

This negative group, together with the diminishing positive group, confirms the opinion that toxin even in these minute amounts tends to stimulate the formation of antitoxin, rather than to use up to any appreciable degree the natural antibodies of the organism.

To carry the investigation a little farther, three children with marked reactions to a 1 to 10,000 solution of toxin were selected, an intradermal injection of the same amount of toxin being given at the intervals of one, four, three, fourteen, fifteen, ten and three days, covering a period of forty days. On one day, April 11, 1916, at the time of the fifth injection, 0.2 c.c. of this solution was also injected into the thigh of each child as a control. The noticeable thing about these reactions is that although the children do not react negatively after the repeated injections, the lesion has been definitely modified. Though it has not become smaller, its duration is much shorter, and in a few days after an injection of toxin, the fourth or fifth day, the stain is the same or less noticeable than it is in the first or second lesion. It is a well-known fact in the manufacture of diphtheria toxin that horses develop a very high-grade local immunity in the tissues surrounding the point of injection of the toxin, and a low-grade general immunity.[6] This is shown by the development of well-marked local necrosis when the same dose of toxin is injected into a remote part of the skin. To guard against this having any influence on the reactions recorded, the injections were made into both arms, and test injections were made into other parts of the skin, such as the thigh, for a control. The changes that have been induced by the successive injections, I believe, are not due to a local skin change. The total amount of toxin used in each of the last three cases was 0.0001 c.c. (minimum lethal dose 0.0015).

6. Smith and Brown: Jour. Med. Research, 1910, xviii, 443.

It has been shown that repeated doses of diphtheria toxin induce immunity in guinea-pigs, but that such immunity does not compare with that induced by toxin-antitoxin mixtures. When toxin alone was used, doses of toxin which were not large enough to produce skin lesions (necrosis and ulceration) were selected. The first doses (Brown[7]) used produced only slight scaling of the skin and little loss of hair. The offspring from such treated mothers showed a resistance to toxin above normal. Amounts of toxin varying from 0.0023 to 0.0098 c.c. (minimum lethal dose 0.007) were injected. Immunity was developed to the point that no local or constitutional reaction was produced by 0.005 c.c. of the toxin. With children, solutions of greater than 1 to 5,000 concentration of our toxin brought about ugly lesions when injected intracutaneously.

The Occurrence of Rashes Following Intradermal Injections of Diphtheria Toxin.—Rashes were observed in five cases, Ula S., Baby G,. Genevieve H., Sarah S. and Loretta B. All of these rashes developed after the second injection, and all appeared on the second or third day after this injection was given. These rashes were erythema in four and urticaria in two. That the rashes were due to repeated injection of toxin is well seen in the cases of Loretta B. and Sarah S. In Loretta B. marked erythematous and urticarial patches appeared on the face, 10 by 25 mm., and on the back, 20 by 30 mm., on three different occasions, always the beginning of the second day after an injection. In Sarah S. the urticaria was very marked, extending over the entire body, and persisting for several days. This occurred on two occasions. Cases showing erythema resembled that shown in Genevieve H., but they were not so marked. Genevieve H. developed a macular erythema, beginning the night of the second day following her second intradermal injection, nine days after her first injection. The eruption extended over the entire body, and was most noticeable on the right side of the face, where a large map-like area, 7 by 7 cm. developed. Several large areas developed on the abdomen, 5 by 5 cm., and several on the arms, measuring 2 by 2 cm. The color was a deep red, and the lips and the lower eyelids were swollen. The posterior cervical glands were enlarged on the left side, but no record of their previous condition had been made. These children had never had similar rashes before.

SUMMARY

It would seem from the foregoing observations that the following conclusions are justified:

7. Brown: Jour. Med. Research, 1912-1913, xxii, 445.

1. Successive intradermal injections of very dilute solutions of diphtheria toxin (0.00001 c.c. L. + dose), when given at intervals varying from five to twelve days, provoke the formation of antibodies, and in those cases already exhibiting a certain degree of immunity, bring about a definite immunity as recognized by the intradermal test.

2. An opinion of the degree of natural immunity may be obtained from the time of first appearance and from the character of the primary intradermal reaction. An early primary reaction of ordinary degree indicates absence, or low degree, of immunity. A late appearing primary reaction indicates that such a person has a greater degree of immunity than one who reacts early.

3. The development of immunity induced by means of infinitesimally small successive doses of diphtheria toxin may be recognized by a hastening in the time of the appearance of the reaction, and a diminishing of the size of the lesion.

4. In those cases in which the size and intensity of the reaction was reduced by successive injections of toxin, the time of the appearance of the reaction was hastened in the large majority of cases observed. The greatest change toward a negative reaction occurred in those cases which gave a primary reaction on the third and fourth day.

5. A primary reacting case which does not change its character after a second, third or fourth intradermal injection may be considered one without any reacting bodies, and, necessarily, one in which diphtheria would be easily induced.

6. The degree of immunity induced by such small doses of toxin as are represented by 0.1 c.c. of highly diluted diphtheria toxin, seems to be very slight, and cannot be compared with the results obtained by the use of toxin-antitoxin mixtures. Solutions carrying sufficient toxin to induce immunity when given intradermally are not well borne by the patient.

I wish to acknowledge the kind assistance of Dr. A. H. Beifeld in confirming many of the measurements and observations made.

THE EPIDEMIOLOGY OF PERTUSSIS

INTRODUCTORY *

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When a group of workers in the Bureau of Laboratories began in 1913 the study of pertussis, we were confronted with an almost complete lack of data bearing on the epidemiology of the disease in New York City.

It was essential, however, for our investigations, especially for the clinical side, that we gather a certain number of facts on the epidemiology of whooping cough, so that we might be in a position to compare the different methods of treatment and obtain a firm basis for our future clinical conclusions and sanitary recommendations.

Early in the fall of 1913, therefore, I began a preliminary survey, which was continued during the spring of 1914 and subsequently extended so as to cover every season of the year and so planned that quite a complete picture of the whooping cough situation for the last three years was obtained.

The material of these surveys is so extensive, however, that it could not be compressed into one article even by eliminating many charts and tables. Hence, it was decided to limit the present communication to the discussion of purely epidemiologic figures in New York, leaving out comparative studies with other cities, the remaining data to be collected in a future article on the symptomatology of the disease.

The present study will be limited to the discussion of the following sub-headings:

Number of cases investigated.
Incidence of pertussis.
The factor of age in pertussis.
The factor of sex in pertussis.
The factor of seasonal variations in pertussis.
The factor of surroundings in pertussis.
Mortality in pertussis.
Sources of infection—carriers—immunity.
Influence of specific vaccines on pertussis epidemiology.
Conclusions and recommendations.

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* Submitted for publication May 22, 1916.
* From the Bureau of Laboratories, Department of Health, New York City.

NUMBER OF CASES INVESTIGATED

The number of cases seen in connection with this study exceeds ten thousand as follows:

Preliminary investigation (1913-1914)	200
Second Survey (Spring and Summer 1914)	1,430
Third Survey (Fall and Winter 1915-1916)	4,200
Hospitals and Institutions	1,900
Whooping Cough Clinic (Aug. 4, 1914-Feb. 1, 1916)	2,600
Private patients and in consultation	182
Total	10,512

Not all of the cases were available for deduction and analysis for each of the principal factors in the epidemiology of pertussis; hence, the exact number of cases investigated will be given when these separate factors are discussed.

INCIDENCE OF PERTUSSIS

Owing to the fact that pertussis has been a reportable disease only since 1900, it is extremely difficult from official records to arrive at any conclusion as to its incidence. Thus, during the years 1900 to 1903 there were more deaths from pertussis in Manhattan and Bronx then cases of whooping cough reported in the whole city of New York, as may be seen from the following figures:

CASES AND DEATHS FROM PERTUSSIS 1900-1902

Year	Greater New York, Cases Reported	Manhattan and Bronx, Deaths from Pertussis
1900	174	318
1901	114	159
1902	348	385

There is no reason why all cases of whooping cough coming to the attention of physicians should not be reported. Placarding, which is the usual deterrent in the reporting of other infectious diseases, is not enforced in cases of pertussis. Continued agitation by educating the private practitioner and keeping the subject before the profession does seem to increase the number of reported cases. This is evident from the number of cases reported during the last three years when pertussis had been discussed in the medical press more extensively than before.

CASES REPORTED FROM 1913-1915 IN THE CITY OF NEW YORK

Year	No. Cases
1913	3,529
1914	3,798
1915	6,868

Of course there will always remain an appreciable number of cases which will not be reported, simply because no physician will be called to attend them. This number also could be reduced to a minimum by public health education, which would constantly point out the danger of neglecting the disease and the necessity of early medical care.

Another error which must be eliminated before the official reports would reflect the actual incidence of pertussis in New York City is due to the comparatively large number of cases which are often reported as whooping cough, when they really are simple colds or nonspecific bronchitis. Such cases are more apt to be reported from school lists and could be easily avoided by reporting as true cases only such as show a paroxysmal cough with vomiting or a whoop; all others should be revisited before being definitely reported.

During our preliminary survey we found only 161 true cases of whooping cough out of 200 cases reported as such. Curiously enough, two cases of mumps were reported as pertussis, the reporter being under the impression that pertussis was the latin name for mumps.

That private practitioners were not the only offenders in failing to report their whooping cough cases was brought out by Billings[1] in 1910, who found that forty-nine out of 116 institutions did not report whooping cough cases and that in only fourteen were new applicants examined before assignment to their respective classes.

In order to ascertain the ratio of unreported cases of whooping cough to those reported, I undertook a short investigation during the last three weeks in November, 1914.

First, tenement houses were visited from which cases of pertussis had been reported, with the following results:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Downtown	19	21	48
Yorkville	14	20	30
Harlem	20	28	61
Bronx	3	8	10
Total	56	77	149

Then houses were visited contingent to those from which cases had been reported. The figures obtained were as follows:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Harlem	10	0	42
Bronx	2	0	3
Total	12	0	45

1. Billings: The Administrative Control of Whooping Cough, Dept. of Health Reprint, Series 1914.

Finally, some houses were visited at random, the results being tabulated as follows:

District	No. Tenements Visited	Cases Reported	Cases Not Reported
Yorkville	3	0	1
Harlem	14	0	16
Bronx	10	0	0
Total	27	0	17

Thus, in ninety-five houses visited there had occurred during the months of August, September, October and part of November, 1914, 288 cases of pertussis of which only seventy-seven, or 26.7 per cent. had been reported. Twelve of the seventy-seven cases, furthermore, were apparently plain coughs, which further decreased the percentage of true cases of whooping cough reported.

Since this investigation, we have collected figures which would indicate that probably only 15 per cent., and by counting adult cases and those of an abortive type, presumably only 10 per cent. of the pertussis cases occurring in New York City are reported.

Under these circumstances the case mortality rate of whooping cough should be revised as soon as more reliable figures are obtained through the reporting of a larger number of cases, although one could not expect the case mortality to become absolutely accurate.

THE FACTOR OF AGE IN PERTUSSIS

The real significance of pertussis as a mortality factor becomes apparent when we study the age of the children who are affected by the disease and who succumb to it. Unfortunately, the department publications do not show any age incidence. We had to draw on our own material.

Thus, of 10,000 cases of pertussis which we analyzed in regard to the age we obtained the following tabulation:

INCIDENCE OF PERTUSSIS ACCORDING TO AGE

Ages	No. Cases	Percentage
Under 1 year	1,940	19.4
1 year, under 2	2,019	20.1
2 years, under 5	4,010	40.1
5 years, under 15	1,799	17.9
15 years and over	232	2.3

It will thus be seen that 80 per cent. of all patients with pertussis were under 5 years of age. At the Whooping Cough Clinic we obtained somewhat similar figures. Among over 2,000 true cases of pertussis, we found the following proportion:

Age	Percentage
Under 1 year	24.3
1 year, under 2	20.8
2 years, under 5	38.6
5 years, under 15	15.1
15 years and over	1.2

TABLE 1.—Deaths from Pertussis in Former City of New York from 1866 to 1915, According to Age Groups and Sex

Year	Total Deaths	Male	Female	Under 1 Year		1 Year and Under 2		2 Years and Under 5		5 Years and Under 15		15 Years and Under 25		25 Years and Under 45		45 Years and Under 65		65 Years and Over	
				Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1866	114	48	66	28	27	16	22	8	15	1	2								
1867	155	65	90	39	45	18	26	8	16	..	3								
1868	217	89	128	53	64	27	43	8	18	1	3								
1869	358	152	206	74	98	46	63	26	39	6	6								
1870	201	79	122	44	61	16	38	18	22	1	1								
1871	465	196	269	103	136	65	78	26	49	2	6								
1872	565	261	304	135	143	66	75	50	72	10	14								
1873	268	117	151	56	79	29	41	31	29	1	1	..	..	..	..	..	1	..	1
1874	489	214	275	110	151	58	69	45	49	1	4	..	..	..	..	..	1		
1875	407	185	222	114	123	50	55	19	40	2	4								
1876	406	178	228	97	113	40	59	35	49	5	6	..	1	1					
1877	440	189	251	98	112	47	75	39	53	5	11								
1878	382	159	223	86	113	37	63	33	42	3	4	..	..	..	..	..	1		
1879	537	253	284	128	132	69	87	49	55	7	10								
1880	277	134	143	64	60	38	53	30	26	2	4								
1881	286	135	151	73	63	33	54	23	30	6	4								
1882	658	289	369	155	187	80	90	46	78	8	13	..	1						
1883	327	169	158	80	88	45	37	35	28	8	3	1	1	..	..	..	1		
1884	490	226	264	131	139	56	68	30	50	9	7								
1885	459	216	279	118	127	57	81	39	62	2	9								
1886	575	261	314	144	159	70	88	40	57	7	10								
1887	188	87	101	49	48	23	30	13	18	2	4	..	..	..	1				
1888	573	238	335	119	163	58	89	47	65	14	17	..	..	..	1				

1889	647	285	362	167	173	67	97	49	81	2	11									
1890	487	213	274	115	133	49	79	40	56	7	6	1	..	1						
1891	352	168	184	95	96	42	44	28	39	3	4	..	..	..	1					
1892	371	156	215	71	104	51	53	32	45	2	8									
1893	542	249	293	122	126	83	95	39	59	5	12	..	..	..	1					
1894	272	103	169	57	76	17	45	26	43	3	5									
1895	496	216	280	114	127	58	92	38	50	5	10	..	1	1						
1896	435	189	246	112	113	42	66	29	57	6	10									
1897	308	132	176	73	87	26	52	31	31	2	6									
1898	442	198	244	105	116	62	70	28	51	3	..	..	6	..	..	..	..	..	1	
1899	350	158	192	74	99	58	40	25	46	1	6	..	..	..	..	..	1			
1900	318	143	175	69	78	38	45	32	41	4	9	..	..	..	1	..	1			
1901	159	65	94	31	43	22	29	11	19	1	2	..	..	..	..	..	..	..	1	
1902	385	175	210	100	111	43	49	28	44	4	6									
1903	187	76	111	41	57	22	29	13	22	..	3									
1904	120	50	70	28	31	10	22	8	15	3	2	1								
1905	239	105	134	51	70	31	33	20	27	3	3	..	.	..	1					
1906	202	95	107	51	54	25	25	17	23	2	5									
1907	201	107	94	59	55	30	16	17	17	1	6									
1908	123	56	67	36	38	14	17	4	10	2	1	..	..	..	1					
1909	254	111	143	57	76	32	35	16	27	5	5	..	..	..	..	..	..	1		
1910	177	77	100	41	54	22	24	12	16	2	5	..	..	..	..	..	1			
1911	256	116	140	67	60	30	40	14	37	5	3									
1912	176	73	103	42	44	20	27	8	26	3	5	..	..	..	..	..	1			
1913	235	101	134	41	69	43	39	14	25	3	1									
1914	175	83	92	48	54	21	23	13	13	1	2									
1915	264	102	162	59	74	28	54	13	28	2	6									
Total	17,046	7,532	9,514	4,019	4,649	2,030	2,629	1,303	1,910	183	288	3	10	3	7	..	8	1	3	

The tabulation shows that nearly 84 per cent. of all pertussis patients were under 5 years of age. These figures prove conclusively that the majority of children who are liable to contract pertussis are under 5 years of age and that 50 per cent. of these are between the ages of 2 and 5.

The deaths according to age for the last fifty years in the former city of New York aggregate the sum of 17,046 (Table 1), distributed as follows:

DEATHS ACCORDING TO AGE FOR THE LAST FIFTY YEARS IN THE OLD CITY OF NEW YORK (MANHATTAN AND BRONX)

Under 1 year	8,668	50.8
1 year, under 2	4,659	27.3
2 years, under 5	3,213	18.8
5 years, under 15	471	2.7
15 years, under 25	13	0.3
25 years, under 45	10	
45 years, under 65	8	
65 years and over	4	
Total	17,046	

This tabulation shows that 97 per cent. of all deaths occurred in patients under 5 years of age, and that over 50 per cent. of all deaths occur in children under 1 year of age. We have seen that the incidence of the disease is about 20 per cent. in that age, which means that while the danger of contracting the disease is relatively slight for children under 1 year of age, the danger of dying from the disease is the highest.

Children of 2 years and under 5, on the other hand, are most liable to become infected, but have the lowest mortality in the group of children under 5 years of age.

Children over 5 and under 15, whose liability of infection is less than those under 1 year, or those of one year and under 2, show a very low percentage (less than 3 per cent.), while all adults show a negligible percentage of deaths (0.3 per cent.), although the rate of incidence, which seems to be only about 2 per cent., is very important when one remembers their rôle of carriers and the tendency of the disease to run an atypical course and hence remain undetected and unreported.

The age ratio is fairly constant and can be ascertained by analyzing any group of cases. The number of deaths, for instance, in the city of New York during 1915 was 385, as may be seen from Table 2, the proportion being as follows: Under 1 year, 52.2 per cent.; 1 year and under 2 years, 30.3 per cent.; 2 years and under 5 years, 14.2 per cent.; total below 5 years, 96.8 per cent.

Figure 1 illustrates the factor of age in pertussis, both as to the incidence and deaths, the former based on 10,000 cases and the latter on over 17,000 deaths.

THE FACTOR OF SEX IN PERTUSSIS

The factor of sex in pertussis is even more remarkable and constant than the factor of age. No matter what set of figures we analyze, we are struck with the high incidence and mortality among girls. In fact, after carefully going over the figures of other diseases I can state unreservedly that it is the only infectious disease attacking both sexes which shows a marked and constant preponderance of deaths and inci-

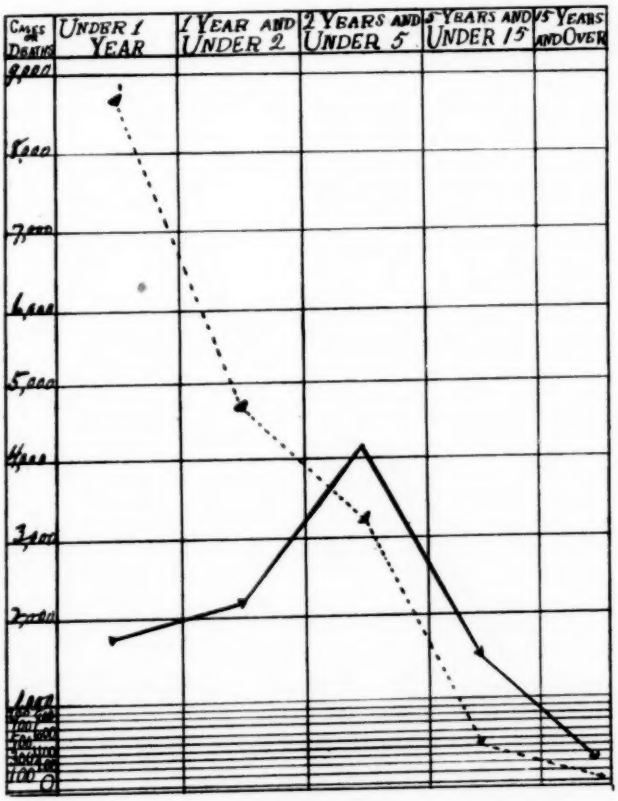

Fig. 1.—Comparative curves of the incidence and mortality of pertussis according to age, based on 10,000 and 17,046 cases, respectively.

dence among girls. This increased severity in girls is probably to be ascribed to anatomical differences in the construction of the larynx and possibly to greater susceptibility of the nervous system of the girl.

The number of cases reported to me from Manhattan and the Bronx from Aug. 4, 1914, to Aug. 4, 1915, amount to 2,711. Of these, 1,180 were among boys (43.5 per cent.) and 1,477 were among girls (54.4 per cent.). The sex of fifty-four (2.1 per cent.) was not reported.

TABLE 2.—Deaths from Pertussis in Greater New York in 1915, According to Weeks, Sex and Age Groups

Week Ending	Total Deaths	Male	Female	Under 1 Year*	1 Year and Under 2	2 Years and Under 5	Total Deaths Under 5	Over 5 and Under 15
January 2.....	2	..	2	1	..	1	2	..
9.....	1	1	..	..	1	..	1	..
16.....	4	1	3	1	2	1	4	..
23.....	5	4	1	3	1	1	5	..
30.....	2	1	1	..	1	1	2	..
February 6.....	4	2	2	4	..	..	4	..
13.....	3	1	2	2	1	..	3	..
20.....	3	1	2	1	2	..	3	..
27.....	6	5	1	5	1	..	6	..
March 6.....	6	5	1	5	1	..	6	..
13.....	4	..	4	3	1	..	4	..
20.....	3	1	2	1	2	..	3	..
27.....	3	..	3	2	1	..	3	..
April 3.....	6	2	4	4	1	1	6	.
10.....	11	3	8	5	2	4	11	..
17.....	15	9	6	8	4	2	14	1
24.....	10	3	7	5	5	..	10	..
May 1.....	10	4	6	5	3	1	9	1
8.....	8	4	4	4	3	1	8	..
15.....	5	3	2	2	1	2	5	..
22.....	9	4	5	7	1	1	9	..
29.....	11	2	9	4	3	1	8	3
June 5.....	7	3	4	3	4	..	7	..
12.....	7	5	2	4	2	1	7	..
19.....	8	4	4	3	4	1	8	..
26.....	12	5	7	5	5	2	12	..
July 3.....	12	5	7	5	4	2	11	1
10.....	7	3	4	3	2	1	6	1
17.....	6	2	4	4	1	1	6	..
24...	9	6	3	5	1	2	8	1
31.....	6	3	3	6	..	..	6	..
August 7.....	13	4	9	7	3	3	13	..
14.....	16	7	9	8	6	2	16	..
21.....	15	6	9	9	4	2	15	..
28.....	7	1	6	3	2	2	7	..

* The deaths occurring in children under 1 year of age was 52.2 per cent. of the whole number of deaths; 1 year and under 2, 30.3 per cent.; 2 and under 5, 14.2 per cent. The deaths occurring in those under 5 years of age was 96.9 per cent.; over 5, 3.1 per cent.

TABLE 2.—DEATHS FROM PERTUSSIS IN GREATER NEW YORK IN 1915, ACCORDING TO WEEKS, SEX AND AGE GROUPS—(*Continued*)

Week Ending	Total Deaths	Male	Female	Under 1 Year*	1 Year and Under 2	2 Years and Under 5	Total Deaths Under 5	Over 5 and Under 15
September 4.....	15	7	8	7	4	3	14	1
11.....	18	6	12	5	11	2	18	..
18.....	12	7	5	8	3	1	12	..
25.....	10	3	7	6	3	1	10	..
October 2.....	12	3	9	1	9	2	12	..
9.....	12	3	9	9	1	1	11	1
16.....	3	..	3	3	..	..	3	1
23.....	6	2	4	4	1	1	6	..
30.....	6	4	2	3	..	3	6	..
November 6.....	4	2	2	1	..	2	3	1
13.....	3	2	1	..	2	1	3	..
20.....	3	..	3	2	1	..	3	..
27.....	5	4	1	4	1	..	5	..
December 4.....	6	1	5	2	2	1	5	1
11.....	4	2	2	4	..	..	4	..
18.....	3	..	3	3	..	..	3	..
25.....	7	1	6	2	4	1	7	..
Total.....	385	157	228	201	117	55	373	12

* The deaths occurring in children under 1 year of age was 52.2 per cent. of the whole number of deaths; 1 year and under 2, 30.3 per cent.; 2 and under 5, 14.2 per cent. The deaths occurring in those under 5 years of age was 96.9 per cent.; over 5, 3.1 per cent.

During the same period we treated at the Whooping Cough Clinic 1,046 patients with true pertussis, of whom 465 (44.4 per cent.) were boys and 581 (55.6 per cent.) were girls. (See Table 3, in which 1,013 of these cases are recorded, there being no record of the age of the remaining thirty-three.)

Out of 8,520 cases which we tabulated according to sex, the proportion seems to be about the same, namely, 3,818 among boys (44.8 per cent.) and 4,702 among girls (55.2 per cent.).

The total number of deaths from pertussis in the former city of New York (Manhattan and Bronx) was, as stated above, 17,046. Of these deaths, 9,514 were among girls (55.8 per cent.) and 7,532 among boys (44.1 per cent.).

Figure 2 illustrates the relative number of these deaths for each year. It is interesting to note that the influence of sex is perceptible in all age periods. Thus, of the 8,668 deaths among patients under 1 year old (Table 1) there were 4,019 among boys (46.36 per cent.) and

TABLE 3.—Incidence of Pertussis and Deaths According to Age and Sex, with Relative Percentage

	Under One Year		One Year and Under Two		Two Years and Under Five		Five Years and Under Fifteen		Fifteen Years and Over		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Cases at the Whooping Cough Clinic:												
Number	98	133	83	90	187	208	94	111	1	8	463	550
Percentage	42.4	57.6	47.9	52.1	47.3	52.7	45.8	54.2	11.1	88.9	45.7	54.3
Incidence as per Epidemiologic Surveys:												
Number	500	838	514	556	1,175	1,343	588	697	12	81	2,849	3,515
Percentage	40.05	59.04	48.03	51.09	46.66	53.33	45.75	54.24	12.90	87.09	44.76	55.23
Deaths in Manhattan and Bronx, 1866 to 1915:												
Number	4,019	4,649	2,030	2,629	1,303	1,910	183	288	7	28	7,532	9,514
Percentage	46.36	53.63	43.35	56.42	40.55	59.44	38.83	61.14	20.00	80.00	44.12	55.87

4,649 among girls (53.63 per cent.); and of the 4,659 deaths among patients under 2 years but over one year old, 2,030 were among boys (43.35 per cent.) and 2,629 among girls (56.42 per cent.). The deaths of those over 2 and under 5 years were 1,303 among boys (40.55 per cent.) and 1,910 among girls (59.44 per cent.). Those over 5 and under 15 years show a disproportion even more pronounced, namely, 471 deaths, of which 183 were among boys (38.83 per cent.) and 288 among girls (61.14 per cent.). It seems that with the accentuation of sex differences there is a higher proportion of deaths among girls as compared with the deaths among boys. Table 3 illustrates the interaction of the two factors of age and sex in both the incidence and number of deaths.

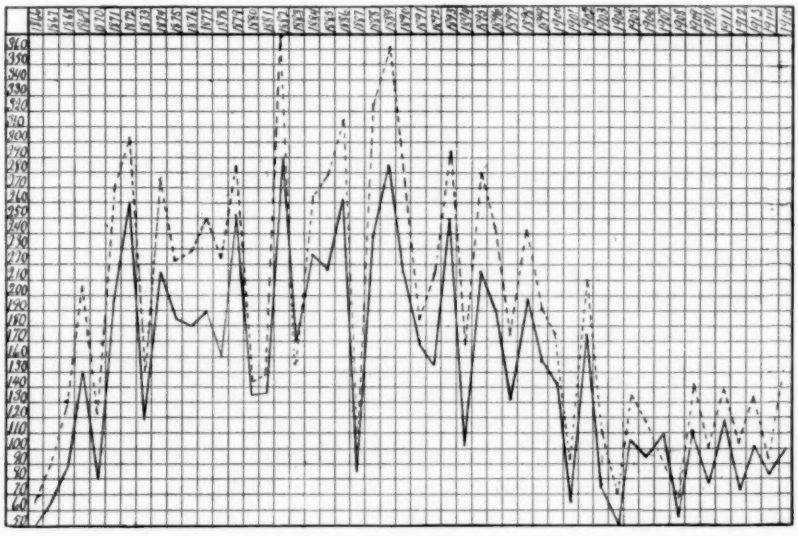

Fig. 2.—Deaths from pertussis in former city of New York for the last fifty years, from 1866 to 1915, according to sex. The solid line represents males, the dash lines females.

In adults there is even a much more marked disproportion between the sexes. Owing, however, to the small number of deaths, and especially to the greater exposure of the woman to infection from children, it would not be wise to draw conclusions specifically supporting the sex factor; but the figures of adult infection as well as mortality strongly suggest that the woman is more prone to contract pertussis and more often succumbs to it than the man.

During our epidemiological survey we tabulated 6,364 cases according to both age and sex. Their interrelation will be best seen in Table 3, where the number of cases at the Whooping Cough Clinic, as well as

the deaths for the last fifty years, are tabulated according to both sex and age.

It is quite apparent from these figures that in children and adults the female is more frequently infected with pertussis at all ages than is the male.

This predisposition to pertussis becomes more significant when we compare our tables to the general birth and death rate. In 1866, there were in Manhattan and Bronx, 10,107 children born, of whom 5,202 were boys and 4,905 girls; in 1912 there were 40,971 boys and 38,954 girls born. Hence, there is a slight excess in the birth of boys over that of girls. It is the same with the general mortality rate. Out of 31,937 deaths in 1880, a typical average year, there were 16,831 among males (rate 28.45) and 15,106 among females (rate 24.45). Of the deaths of those under 5 years, 7,912 were among boys (rate 111.7) and 6,738 among girls (rate 96.4). In 1912 there were 43,492 deaths, of which 12,819 were among those under 5 years of age, namely 7,050 boys (death rate 44.3) and 5,769 girls (death rate 36.9).

When we turn now to the mortality tables of other infectious diseases which mostly attack children, we find that in none of them is the sex factor of any significance.

In measles, for instance, there are generally more deaths among male than among female patients. In scarlet fever the mortality is variable; some years the deaths among female patients predominate, in others, those among male patients; as a whole there are more among male patients. In diphtheria and croup the same relations exist with a decided increase of deaths among boys under the age of 5. Deaths from bronchitis vary each year, but when several years are taken, there are decidedly more deaths among male patients; of those under 5 years of age, there is constantly a larger number of boys dying. In pneumonia this excess of deaths among males over those among females is even more pronounced.

Hence, we must consider pertussis as an exception to other infectious diseases by the constancy with which it attacks girls and the predisposition which girls seem to have to succumb to the infection more readily than boys.

THE FACTOR OF SEASONAL VARIATIONS IN PERTUSSIS

The relation of the seasons to the prevalence of pertussis is seemingly paradoxical. In its etiology, symptomatology and course, whooping cough is apparently an infection of the upper respiratory tract, and one would therefore expect it to be most prevalent and fatal during the fall and winter months. During our epidemiologic surveys it was found, however, that the actual state of affairs was just the opposite, most cases being reported during the spring and summer and most deaths occurring in the middle of the summer.

Thus, the 6,868 pertussis cases reported during the year 1915 were distributed as follows:

Month	Cases Reported	New Cases at Clinic	Deaths
January	341	140	14
February	381	65	16
March	452	91	16
April	462	112	42
May	754	114	43
June	599	231	34
July	843	253	40
August	906	348	51
September	640	295	55
October	543	181	39
November	458	173	15
December	389	157	20
Total	6,868	2,160	385

It will be seen from the above table that the number of new cases treated at the Whooping Cough Clinic was highest in August. It should be noted, however, that the relatively greater ease with which the clinic can be attended during the summer months might have slightly influenced the clinic figures; also that a certain percentage of these clinic cases were not true cases of pertussis.

The various surveys convinced me that most cases of pertussis seem to occur in the spring and summer. For obvious reasons no figures which would have any comparative value could be given here, as the investigations were not conducted during the whole of any year or month.

Figure 3 illustrates the number of cases reported to the department for the last ten years and also the number of deaths. It will be seen that the incidence seems to be largest in the spring; but it must be remembered that the morbidity records of pertussis are noncomparable and that many pertussis sufferers leave the city during the summer months for the seashore and hence are not reported. Complete returns would probably show the curve of morbidity reaching its acme in July, a few weeks before the height of the mortality in August.

The remarkable feature of the pertussis curve is that it coincides in most years more nearly with that of the diarrheal diseases rather than with that of the respiratory infections.

Figure 4 illustrates the seemingly opposite effect which the seasonal variation has on pertussis as contrasted to its effect on the mortality of scarlet fever, measles, diphtheria and croup and acute bronchitis. It will be seen that the lowest point reached by the curve of acute bronchitis coincides with the highest point of the curve of pertussis.

In the face of these facts, one must ask himself involuntarily whether the fatality of pertussis is not due to something besides the respiratory infection; whether a toxin similar to that produced by the

diarrheal diseases is not the direct cause of death. Another view would be that death during the summer is hastened by gastro-intestinal complications and that during the winter bronchopneumonia is the usual complication. The question is now being studied through careful analysis of the death certificates and other data. Judging from the death certificates one would say that diarrheas complicate only a relatively small number of pertussis cases.

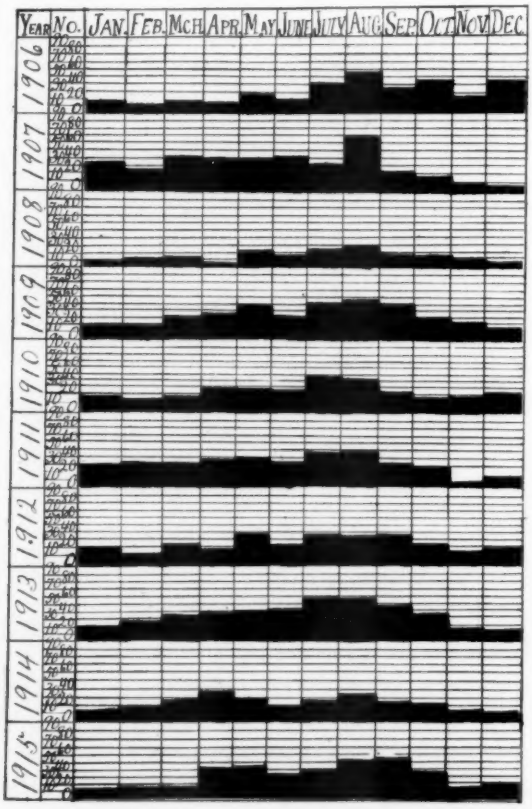

Fig. 3.—Deaths from pertussis by months for the last ten years, from 1906 to 1915.

THE FACTOR OF SURROUNDINGS IN PERTUSSIS

Most of the cases included in this study are of patients living in congested tenement districts, where the opportunities of infection are constant and many guardians are ignorant of the danger of the disease and its prevention.

Out of 162 investigated deaths, 160 occurred in tenement houses or in institutions to which these tenement patients were transferred after the onset of pneumonia. In all these cases there were more than three children in the family and in seventy-four the mother had to go out

working and leave the children in nurseries or in the care of neighbors. The average number of rooms occupied by the family is a little less than two and a fourth, a large number occupying only one or two rooms.

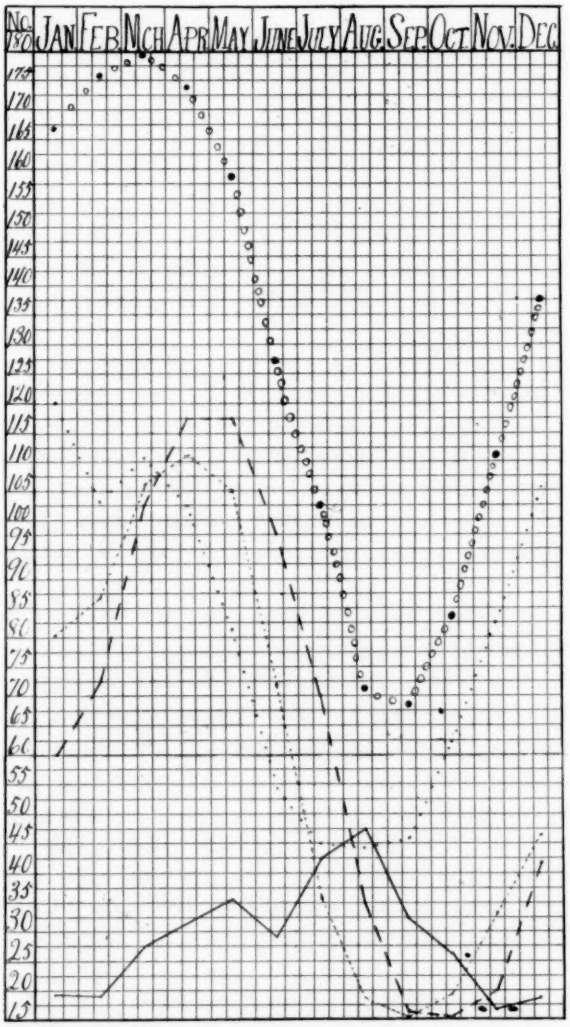

Fig. 4.—Average yearly deaths from certain infectious diseases by months, for the decade 1905 to 1914. Solid line indicates pertussis; line of long dashes, measles; short dashes, scarlet fever; dotted line, acute bronchitis, and the line of rings, diphtheria and croup.

Although I have no extensive data on the subject, it is my impression as I examine case after case at the Whooping Cough Clinic that the children who whoop longest and most severely lack sufficient fresh air and suffered from malnutrition before they contracted pertussis.

Of the 182 cases in private practice, there was not a single death, although many of them were very severe and several patients contracted pneumonia. Fresh air seemed to have a decidedly favorable effect on the course of the disease.

Apparently, it is not the fresh air per se which is so effective, but the change of air. Change of surroundings in themselves seem to have a beneficial effect, even if the amount or quality of the air is not appreciably different from the former surroundings. To this fact may perhaps be ascribed the prevalent "superstition" that the neighborhood of gashouses is beneficial to pertussis.

We often see patients at the clinic who reside in Manhattan tenements and who have relatives in East New York living in equally congested districts or vice versa, and a visit from one congested district to another seems to be so beneficial that it is often extended until the patient stops whooping.

Two patients with pertussis, said to have contracted the disease on a transatlantic liner (probably not on the liner, but on land before sailing), stopped whooping when they set foot in New York. Another, who apparently developed pertussis on a steamboat, began to whoop two days after landing and was severely ill for four weeks without improving in spite of a well-ventilated, sunny room. He was finally taken to Lakewood, where the paroxysmal cough subsided a day after arrival.

It seems, therefore, that the ideal place for the treatment of pertussis patients would be a ferry-boat with open wards on the decks and which could make occasional trips to different points of the harbor. Such a ferry could also be moored to certain piers and clinics held for pertussis sufferers in the neighborhood. Such a boat camp, to my estimation, would solve the problem of efficiency caring for the numerous patients having whooping cough in the city, especially during the summer months. A hospital for pertussis patients only and specially designed for the purpose would be the next choice.

In sparsely populated districts, like the boroughs of Richmond and Queens, there is apparently very little pertussis.

MORTALITY IN PERTUSSIS

For reasons sufficiently discussed before, it is extremely difficult to arrive at the actual case incidence mortality. The failure to report all cases of pertussis, and especially the mild atypical cases, precludes the possibility of arriving at complete statistics on the subject.

During the preliminary survey we found, for instance, seven deaths out of 161 actual pertussis cases, which gives a case mortality of 4.3 per cent. Of all cases investigated during the last three years, we find that there is a record of 210 deaths out of 8,310 cases; but in view of

the irregularity as to the seasons and the impossibility of revisiting these patients, hardly any account of these figures can be taken.

A more accurate, though incomplete, estimation may be made by comparing the number of deaths from whooping cough in the city of New York in 1915 with the number of cases reported. These figures are 385 and 6,868, respectively, and show a case mortality of 5.60 per cent. The actual case mortality, when one takes into consideration the unreported and atypical cases and those among adults, is probably from ½ to 1 per cent.

As to the relation of pertussis to the general death rate, it may be studied from Table 4, which gives the death rate of pertussis per 100,000 population in the former city of New York (Manhattan and Bronx) also the annual deaths and death rate per 1,000 population since 1868.

TABLE 4.—PERTUSSIS DEATH RATE AS COMPARED TO GENERAL DEATH RATE, FORMER CITY OF NEW YORK

Year	Population	Total Deaths	Death Rate per 1,000 Population	Deaths from Whooping Cough	Rate per 100,000 Population
1868	851,137	24,889	29.24	217	25.50
1869	896,034	25,167	28.08	358	39.96
1870	943,300	27,175	28.80	201	21.31
1871	955,921	26,976	28.22	465	46.65
1872	968,710	32,647	33.70	565	58.32
1873	981,671	29,084	29.63	268	27.31
1874	1,030,607	28,727	27.89	489	47.47
1875	1,044,396	30,709	29.40	407	38.97
1876	1,075,532	29,152	27.11	406	37.76
1877	1,107,597	26,203	23.66	440	39.76
1878	1,140,617	27,008	23.67	382	33.50
1879	1,174,621	28,342	24.13	537	45.72
1880	1,209,196	31,937	26.42	277	22.92
1881	1,244,511	38,624	30.75	286	22.98
1882	1,280,857	37,924	29.61	658	51.38
1883	1,318,264	34,011	25.81	327	24.81
1884	1,356,764	35,034	25.83	490	36.12
1885	1,396,388	35,682	25.56	495	35.45
1886	1,437,170	37,351	26.00	575	40.02
1887	1,479,143	38,933	26.33	188	12.71
1888	1,522,341	40,175	26.39	573	37.64
1889	1,566,801	39,679	25.36	647	41.30
1890	1,612,559	40,103	24.87	487	30.20
1891	1,659,654	43,659	26.31	352	21.21

TABLE 4.—Pertussis Death Rate as Compared to General Death Rate, Former City of New York—(*Continued*)

Year	Population	Total Deaths	Death Rate per 1,000 Population	Deaths from Whooping Cough	Rate per 100,000 Population
1892	1,708,124	44,329	25.95	371	21.72
1893	1,758,010	44,486	25.30	542	30.83
1894	1,809,353	41,175	22.76	272	15.03
1895	1,873,201	43,420	23.18	496	26.48
1896	1,906,139	41,622	21.84	435	22.28
1897	1,940,553	38,877	20.03	308	15.87
1898	1,976,572	40,438	20.46	442	22.36
1899	2,014,330	39,911	19.81	350	17.38
1900	2,055,714	43,227	21.03	318	15.47
1901	2,118,209	43,304	20.45	159	7.50
1902	2,182,836	41,704	19.11	385	17.64
1903	2,249,680	41,776	18.57	187	8.31
1904	2,318,831	48,743	21.02	120	5.17
1905	2,390,041	45,199	18.91	239	10.00
1906	2,460,456	46,108	18.74	202	8.21
1907	2,534,454	47,698	18.82	201	7.93
1908	2,612,322	44,061	16.82	123	4.71
1909	2,694,373	44,387	16.47	254	9.43
1910*	2,777,542	45,628	16.44	177	6.76
1911*	2,849,635	45,324	15.91	256	8.98
1912*	2,921,728	43,492	14.89	176	6.02
1913*	2,993,821	43,189	14.43	235	7.85
1914*	3,065,914	43,253	14.21	175	5.71
1915*	3,138,007	43,794	13.96	264	8.41

* Corrected population figures as per U. S. census estimates.

It will be seen that the death rate has steadily decreased from 25.5 per 100,000 population to about 7. It is interesting to note that it went up as high as 58.82 and that it was frequently four to five times its present rate. The lowest rate was 4.71 in 1908. Besides the general tendency toward a lower death rate, no rhythm of any kind can be discerned; the number of deaths for each seems to be independent of any meteorologic or other uncontrollable agencies. The steady lowering of the death rate is probably due to the general increase in knowledge and observation of public and personal hygiene.

One cannot refrain from comparing this lowering of the pertussis death rate with that of diphtheria. Although no specific therapy had been used in whooping cough until recently it compares favorably with the diphtheria curve influenced by antitoxin.

SOURCES OF INFECTION—PERTUSSIS CARRIERS

The sources of infection in whooping cough are in the majority of cases easily ascertained. In a certain percentage of cases, however, it is obscure and can only be determined after a painstaking investigation. Only in a very limited number of apparently sporadic cases does the source of infection remain undiscovered. Those baffling cases escape detection only through lack of intelligent observation on the part of the guardian.

The infection in pertussis is undoubtedly transmitted through direct contact. While infection through the common use of pencils and other personal articles may and probably does occur, there is always enough personal contact between the diseased and the healthy child not to exclude direct transmission as well as indirect infection.

At the suggestion of Dr. Williams, special attention was paid, in our epidemiologic investigation, to the presence of domestic animals in the houses of those suffering from pertussis. Out of 1,120 homes visited, we found only twenty-six which harbored such pets, namely, fifteen dogs, eight cats, one rabbit, one monkey, one turtle. With one exception, none of these animals had any cough, and in view of the fact that we have been unable so far to transmit pertussis to puppies and rabbits, it is hardly probable that these animals could become factors in the transmission of the disease. One dog (a Newfoundland) was found in a Staten Island home to have a hoarse cough; but the animal had been sick with rheumatism for nearly a year. I asked permission to take a culture from the dog's throat, having in mind the *Bacillus bronchisepticus,* which morphologically resembles the Bordet-Gengou bacillus; but owner refused, stating he did not believe in "vivi-section." Two weeks later he telephoned me that he was willing to let me take the culture, but I was unable to go out that day, and the dog died the following morning.

At the Whooping Cough Clinic a careful record was kept of the alleged sources of infection. The analysis of 2,310 actual cases of pertussis gives the following results:

Probable Source of Infection	No. Cases
Neighbor	1,311
Relative or friend	204
Playmate	203
School	146
Nursery	76
Moving pictures	62
Recreation pier	18
Roof garden	9
Ferry	8
Street (?)	6
Subway, elevated and street cars	4
Unknown	263
Total	2,310

Thus, nearly 60 per cent. of all sources of infection were ascribed to neighbors' children who were suffering from the disease. The next two largest figures, but only about 10 per cent. each of the total, are blamed on relatives and playmates. The school was accused in only about 7 per cent. of the cases. An interesting though small factor seems to be the recreation piers, roof gardens and ferries, where people usually go to escape the infection of the crowded tenement.

The moving-picture shows as sources of infection became the subject of a special investigation. During the spring, summer and autumn of last year I visited off and on quite a number of cinematograph shows and found them to be ideal dissemination grounds for pertussis and possibly other diseases.

The better class of cinemas, in the central part of the city, do not admit children in arms; but the 5-cent shows, which are fortunately decreasing in number, and also some 10-cent places in the congested districts on the East Side, Brooklyn, Harlem and the Bronx, cater to the family trade, and many of them have as a special convenience for their patrons a "baby carriage garage." The baby is either left in the carriage or taken inside; the other children are invariably taken in unless they are too sick to leave their beds. It is rare in visiting some of these crowded shows not to hear continued coughing, from the short, plain, bronchial cough to the long-drawn-out, severe whoop. Table 5 will give one an idea of the actual state of affairs.

TABLE 5.—CINEMAS AS SOURCES OF INFECTION

Month, 1915	Number of Cinemas Visited	Number of Children Whooping	Number Having Paroxysmal Cough	Number Having Plain Cough	Number of Adults Coughing	Number Cinemas Using Atomizers
March	10	1	5	6	2	8
June	14*	2	2	8	0	4
July	12†	2	0	5	1	1
September	20‡	5	11	2	8	5
October	15	2	2	4	22	10
November	14	0	1	2	30	6
December	9	0	0	8	52	8
Total	94	12	21	35	63	42

* Four open air. † Ten open air. ‡ Three open air.

Another objectionable feature of these shows is the use of the so-called perfume atomizer tabulated in the last column of Table 5. It is operated by one of the attendants, whose duty it is to spray the premises at regular intervals during the performance. He walks up

and down the aisles using as much strength as possible, so that the perfume may reach at least to the center of the row of seats. It does not require much imagination to see how the sputum droplets from a child who coughs may be carried by these vigorous air currents to an unlimited number of spectators. Besides this, a false feeling of security is promoted among the public by disguising the foul air and thereby discouraging the proper ventilation of the premises.

Crowded cars as possible sources of infection were brought to my attention by the following case: A woman with two children boarded a Second Avenue elevated train at 105th St., and sat opposite another woman with three children who looked perfectly normal. A few stations farther downtown one of the children began to whoop and was taken care of by the mother, who put a handkerchief in front of his mouth and bent his head to the floor. Presently the second and then the third child began to cough and vomit, and she naturally could not attend to all of them at once. The car being crowded, it was impossible for the woman with the two healthy children to alight before 59th St. About two weeks later she applied to the Whooping Cough Clinic for treatment and gave the above history of infection.

Of the 263 cases of pertussis whose source of infection was not known by the parent, I visited about ninety. Nearly all of these, after careful cross examination of the parents, could be ascribed either to a neighbor's child or to some friend whose visit had been forgotten.

Carriers.—Eight patients undoubtedly were infected by the kiss of adults whose children had the whooping cough but had never been in contact with these patients, as they lived in different parts of the city. All these adults had a "little cough," which lasted for five or six weeks, and had all the earmarks of typical carriers.

An interesting pertussis carrier was Peter G., who boarded with his sister in Harlem. Two nieces and one nephew contracted whooping cough from their neighbors and Peter began to cough a few weeks later. About the beginning of March he visited a sister living in Brooklyn with the view of reconciling her to the Harlem sister, from whom she had been estranged. About eight days later one of the children began to cough. March 10 the Brooklyn sister visited her Harlem relative alone, made up with her and told her of her children, who were whooping. Both sisters finally met at the Whooping Cough Clinic a week later. In the meantime, Peter left his Harlem sister and went to live with his brother, who had just come from some Pennsylvania town; he was still coughing. A week later one of this brother's children began to cough and a few days later started to whoop and vomit. The other child had had whooping cough before. The father now accused Peter of having given the disease to the child and they quarreled, Peter going to live with a cousin (a bachelor) in East Twelfth

St. On April 14 one of the neighbor's children began to whoop, and as there was no pertussis cases in that house, we finally traced the source of infection to Peter, who was still coughing, and asked him for his sputum. This he delayed until April 20, when he sailed for Italy, having enlisted in the army. He sent a sputum jar to the laboratory on that day, but it was found later that it was his cousin's sputum, who was perfectly normal. The child who had contracted pertussis from Peter told me that Peter often kissed her and gave her pennies because she looked so much like his niece in Harlem. We have surnamed this carrier "Pertussis Pete," and trust that he will be spared by the enemy and return to New York so that we may complete our records.

Natural Immunity.—During the preliminary survey I was impressed with the apparent immunity that children of all ages seemed to exhibit. Thus, out of ninety-two families visited in which whooping cough had occurred I found that in twenty-seven of them (29.3 per cent.) there were one or more children of susceptible age who had failed to contract the disease. Subsequently, however, it was found that in the great majority of these cases, after careful cross examination, a history of a mild cough without the characteristic paroxysms could be obtained; many of them having had vomiting spells which had been forgotten by the parents. A certain number of these apparently immune children could also be ruled out because of their slight contact with the infected ones or entire absence from home during the attack. Nevertheless, there seems to be a certain indefinite percentage who do not contract the disease or who do not show any symptoms of it.

Of a total of 840 families (3,100 children) visited and questioned with the subject of natural immunity in view, I found 270 (914 children) in which one or more children had had apparently atypical attacks of the disease; 61 of these children were apparently immune; 42 had had pertussis before and the rest (811) were probably abortive cases. Among these 811 there were 69 who had had whooping cough before.

As a contrast I found only 18 children among 9,400 with an apparent second attack of pertussis (with typical whoop).

INFLUENCE OF SPECIFIC VACCINES ON THE EPIDEMIOLOGY OF PERTUSSIS

The pertussis stock vaccines as prepared in the Bureau of Laboratories have not been long enough used or in sufficiently general use to lend themselves to deductions regarding their influence on the morbidity or mortality. One impression, however, has been that, judging from the results obtained at the Whooping Cough Clinic and by about forty private physicians and health officers in this and other cities, they have undoubtedly reduced the number of deaths and prevented the spread of the disease.

The good results reported last year by myself[2] have continued, and when the proper vaccines are used, there has been a further shortening of the paroxysmal stage and a reduction in the severity and number of the paroxysms. Dr. Hoag, in charge of the Children's Clinic at St. Mary's Hospital and Dispensary, in a paper read before the Bellevue Hospital Alumnae Association, has reported a large number of patients who have been cured and many in whom the disease has been prevented by our vaccines; his results, owing perhaps to a better class of patients, have been even more brilliant than those at the Whooping Cough Clinic.

Out of 2,103 patients with pertussis, 75 per cent. of whom were treated with vaccines and were followed up by the Clinic nurse, we had fourteen deaths. Ten of these were treated by drugs and one injection of the vaccine. The other four were treated by vaccines exclusively, two of them being commercial mixed vaccines and two others our laboratory stock vaccines. These two died in convulsions. Four more deaths occurred at the Reception Hospital, but the patients had been brought to us moribund and we can draw no conclusions whatever from their deaths except that neglected nursing at home (mothers had to go out working) probably contributed to the fatal outcome.

We have not had a single death in patients brought to us before the third week of the paroxysmal stage and who presented themselves for vaccine treatment at regular intervals. This fact alone seems to warrant the establishment of more Whooping Cough Clinics.

As to prophylaxis, while we still lack the absolute proof that pertussis vaccine is a positive prophylactic agent, data are accumulating which strengthen our belief that it acts as such in all patients who are inoculated before any symptoms develop and that in many cases it aborts the disease. Whether such prophylactic cases would have remained free from pertussis even without the administration of the vaccine is a question which cannot be solved in private or dispensary practice.

SUMMARY

Epidemiologic studies in Whooping Cough conducted by the Research Laboratory shows that pertussis is a very prevalent disease in New York City, and that probably only a tenth of all cases are reported to the Department of Health.

About 80 per cent. of all cases and 97 per cent. of all deaths are in children under 5 years of age. Fifty per cent. of the cases are in those under 2 years of age, and over 50 per cent. of all deaths are in children under 1 year of age.

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2. Luttinger: Whooping Cough, Its Treatment and Prophylaxis, Based on the Bordet-Gengou Etiology, New York Med. Jour., May 22, 1915.

The incidence of pertussis among girls, as well as the number of deaths, is constantly higher than among boys, the proportion of both morbidity and mortality being about 44 per cent. for boys and 56 per cent. for girls.

In contradistinction to other respiratory diseases, whooping cough seems to be most prevalent in the spring and summer months and the mortality curve reaches its highest point in August, showing a similarity to the diarrheal diseases, although most deaths are due to pertussis pneumonia.

Poor surroundings, congestion, lack of fresh air and proper care due to the guardian's precarious economic status seem to have a determining effect on both the morbidity and mortality of pertussis.

The actual case mortality in whooping cough is difficult to estimate, owing to incomplete returns; it is probably about 1 per cent. The death rate per 100,000 population is about 7. It has been steadily decreasing for the last fifty years having been as high as 58.82 in 1872 and as low as 4.71 in 1908.

Whooping cough is transmitted by direct contact and in nearly 60 per cent. of cases the source of infection is given as coming from a neighbor. Relatives and friends, schools, nurseries, recreation piers and ferries are other sources of infection. Moving picture shows and public conveyances seem to be important factors in the dissemination of the disease.

Adult pertussis carriers probably have been disseminating the disease and have remained unrecognized owing to the atypical form in which it manifests itself.

Pertussis vaccines, as prepared by the Bureau of Laboratories, when given early, have continued to give good curative and prophylactic results at the Whooping Cough Clinic and in the hands of a large number of private practitioners and health officers. The very small number of deaths under vaccine treatment and the vast crowds who apply for treatment at the clinic indicate a favorable and possibly tangible influence of the specific treatment on the further epidemiology of the disease.

CONCLUSIONS

Measures should be adopted to reduce the morbidity and mortality of pertussis, special attention being paid to children under 1 year of age in the spring and summer months. These measures should include the following:

1. Education of the private physicians as to the prevalence and fatality of the disease and the securing of his cooperation in reporting all pertussis cases and in using the specific vaccines wherever practicable as a prophylactic and in early cases.

2. The education of the laity through physicians, nurses, leaflets, etc.

3. Regulation of moving-picture shows and other public meeting places, which should as far as possible exclude children with paroxysmal coughs.

4. Quarantine of pertussis cases during the first two weeks of the disease.

5. The establishment of more whooping cough clinics, at least one in each borough.

6. The organization of a boat camp for the rational treatment of pertussis, especially during the summer time, should be carefully considered.

7. The use of a suitably constructed pertussis hospital, in which the care of patients with severe attacks of whooping cough could be more efficiently undertaken and which would afford an opportunity for further scientific research on laboratory as well as clinical lines.

My thanks are due to Mr. J. H. Gibbons of the Bureau of Records for statistical transcriptions from the Department of Health records and for other courtesies. To the Misses Loretta Smith and Florence Walters, the very efficient nurses of the Whooping Cough Clinic, who did most of the follow-up work, I am greatly indebted for the successful completion of this study.

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AN ANAPHYLACTIC SKIN REACTION TO DIPHTHERIA BACILLI *

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The intracutaneous toxin test of Schick for antitoxic immunity in diphtheria may be stated to have definitely established itself as a safe, easily applied and reliable practical test for detecting those persons who have sufficient natural diphtheria antitoxin in their body fluids to protect them against this infection and also as a measure of antitoxin production after active immunization with toxin-antitoxin mixtures, the latter being the original purpose of Schick in working out the technic of this test to replace the more expensive, time consuming and laborious procedure of determining the antitoxin content of a serum by means of injecting mixtures of the serum and a toxin into guinea-pigs.

The positive toxin reaction is a localized inflammation excited by the unneutralized toxin in the skin, and in the majority of instances the area of erythema and edema is sufficiently well marked at the end of forty-eight hours to permit the proper interpretation of the test.

The practical value of the test, however, is impaired by the occurrences of false reactions among immune and nonimmune persons alike, first described by Park, Zingher and Serota,[1] and regarded by them as being local anaphylactic reactions to the protein of the broth and autolyzed diphtheria bacilli contained in the toxin broth. To this reaction they have applied the term "pseudo Schick reaction."

As the skin is a very delicate reacting medium, inflammatory reactions may be caused by a variety of factors. In a study of pseudoreactions with particular reference to those caused by trauma and the protein constituents of the broth alone[2] we found that trauma due to the injection of a fluid containing a preservative into the epidermis of persons whose skins are for some reason unduly sensitive plays an

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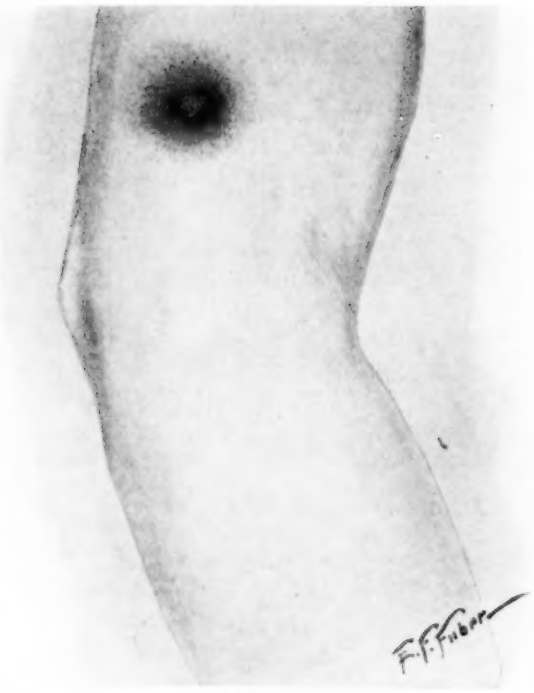
* From the McManes Laboratory of Experimental Pathology of the University of Pennsylvania and the Laboratory of the Philadelphia Hospital for Contagious Diseases.

1. Park, W. H., Zingher, A., and Serota, H. M.: The Schick Reaction and Its Practical Application, Arch. Pediat., 1914, xxxi, 481.

2. Kolmer, J. A., and Moshage, E. L.: A Note on the Occurrence of Pseudoreaction on the Skin with Special Reference to the Schick Toxin Test, Jour. Am. Med. Assn., 1915, lxv, 144.



Positive diphtherin reaction in M. A., aged 6 years; pustular reaction seventy-two hours after the intracutaneous injection of 0.1 c.c. of diphtherin. The patient reacted negatively to the Schick toxin test.

Illustrating Article by John A. Kolmer, M.D., with the assistance of Emily L. Moshage, M.D.
American Journal of Diseases of Children, September, 1916

important part in the production of slight inflammatory reactions. As pointed out by us, this condition of peculiar skin hypersensitiveness was found especially among persons suffering or convalescent from scarlet fever and measles.[3] Likewise the amount of fluid injected was found to influence the percentage of pseudoreactions, fewer being observed when the proper dose of toxin was contained in 0.1 c.c. than in 0.2 c.c. Furthermore, the sharp, stinging pain experienced during the injection, when it is properly given intracutaneously, is much less with 0.05 or 0.1 c.c. than with 0.2 c.c. For these reasons we dilute our toxin for the Schick test in such manner that the proper dose is contained in 0.1 c.c. of fluid.

The amount of protein substances injected in the broth used in the preparation of toxin was found to have less influence on the question of false reactions than the total amount of fluid injected. Reaction to the protein substances and various extractives from veal and beef may be due to their purely irritative character or to a general and nonspecific anaphylactic-like reaction explainable on the basis of the hypothesis advanced by Jobling and his colleagues that these substances may bring about a local release of proteolytic ferments by removing through absorption the unsaturated fatty acids or antitrypsin, followed by the digestion of the patient's own serum protein and the formation of toxic substances capable of producing an inflammatory reaction.

The reactions due to trauma and the substances contained in broth are rather poorly colored and defined, irregular in outline, measuring roughly about 0.5 by 0.5 cm., but being sometimes much larger, and accompanied by slight edema. The great majority subside within forty-eight hours, and for this reason the Schick test should not be read within the first twenty-four hours after the injection of the toxin.

It is apparent, therefore, that one variety of the pseudoreaction due to trauma, skin hypersensitiveness, and the various constituents of broth may be limited to some extent by attention to such details as the employment of a fine needle; a highly potent stock toxin that requires high dilution in order to obtain the proper dose for the Schick test, thereby reducing the amount of broth constituents injected; the injection of a minimum amount of fluid and waiting whenever possible for forty-eight hours before reading the results.

Of greater interest are the allergic or anaphylactic reactions to the protein of the diphtheria bacillus. The disease diphtheria is so widespread and so large a proportion of persons carry or have carried diphtheria bacilli in the nose, throat or ears that it may be well expected that a large number of persons will exhibit a condition of hypersensitiveness to the diphtheria protein.

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3. Kolmer, J. A., and Moshage, E. L.: The Schick Toxin Reaction for Immunity in Diphtheria, Am. Jour. Dis. Child., 1915, ix, 189.

We were influenced toward making the studies recorded in this paper not only on account of the general importance of allergy in diphtheria, but also on the basis of the claims set forth by Gay and his associates that allergic skin reactions may be regarded as an index to immunity. If this is true it may be possible to shed more light on the immunity in diphtheria by means of an anaphylactic or allergic skin reaction, and show that resistance to diphtheria is not entirely or purely antitoxic in character and explain in part why some persons who give a positive Schick reaction do not contract diphtheria even though exposed to this infection.

MATERIALS AND METHODS OF STUDY

In this investigation we have conducted the anaphylactic skin reactions with an emulsion of washed and heat-killed diphtheria bacilli, for which we propose the name "diphtherin"; at the same time the regular Schick test was conducted in each person.

Preparation of Diphtherin.—The diphtherin used in this study was prepared of forty-five different strains of diphtheria bacilli freshly isolated (from three to thirty days previously) from the throats, noses and ears of persons suffering with diphtheria and convalescent from this infection. The types of bacilli contained thirty-three cultures of granular types, eight cultures of long, solid types, and four cultures of short, solid types.

Each culture was grown in glucose broth for four days and all mixed in a single flask and shaken mechanically with glass beads to break up clumps. To each 100 c.c. of the emulsion was added 5 c.c. of sterile horse serum antitoxin (2,500 units) and the whole shaken at room temperature for four hours. After this time the emulsion was placed in sterile centrifuge tubes and the bacilli separated and washed twice with large volumes of sterile normal salt solution. After the final washing the bacilli were resuspended in sufficient sterile salt solution to make, after thorough shaking, about two billion bacilli per cubic centimeter. This emulsion was heated at 60 C. for an hour, cultured for sterility and preserved with 0.2 per cent. tricresol. Subcutaneous injection of 1 and 2 c.c. into 250-gm. guinea-pigs showed absolutely no evidences of local reaction or general toxemia. In conducting the test, 0.1 c.c. of the emulsion was injected intracutaneously in the arm.

Preparation of Toxin.—The toxin for the Schick test was prepared by diluting a toxin (L + dose 0.625 c.c.) 1 to 100 with normal salt solution and determining the minimal lethal dose in a series of guinea-pigs weighing from 250 to 300 gm.; one-fortieth this amount was used

as the dose in conducting the toxin test. Sufficient normal salt solution containing 0.25 per cent. tricresol was added to dilute the dose of toxin to 0.1 c.c., which amount was injected intracutaneously.

THE DIPHTHERIN REACTION

All reactions were recorded after an interval of forty-eight hours following injection, in order to permit the subsidence of the purely irritative reaction due to trauma, as previously pointed out.

Two types of reactions were observed. The first resembled the luetin reaction in all its essential details, being a circumscribed area of erythema accompanied by marked edema. The majority of these reactions were popular in character, while some were distinctly pustular (see accompanying figure). The height of reaction was usually reached in from forty-eight to seventy-two hours, when subsidence began, to be followed by a small reddish nodule which persisted for several days.

The second type of reaction corresponded quite closely with that described by Park and Zingher, being of early development (maximum in twenty-four hours) and marked by a wide and poorly circumscribed pinkish zone or cutaneous blush, with a smaller and redder area about the site of injection. This type of reaction when once seen is comparatively easy to distinguish from the true Schick toxin test, while it is frequently impossible to differentiate between the former type of diphtherin and the toxin reactions.

The Schick reactions were characterized by areas of erythema, with a brownish tinge measuring from 0.5 to 2 cm. in diameter and accompanied by slight edematous infiltration of the underlying tissues. After from forty-eight to seventy-two hours these reactions began to fade, leaving a pigmented area with slight superficial desquamation.

In a number of instances the toxin reaction showed a wide area of cutaneous blush, with a smaller area about the site of inoculation of deeper erythema with a brownish tinge and marked edema. All persons reacting in this manner gave positive reactions to the diphtherin alone and indicated thereby that the reactions to the toxin were a combined toxin and anaphylactic response.

THE DIPHTHERIN REACTION IN PERSONS OF VARIOUS AGES

The diphtherin and toxin tests were applied to 188 persons of various ages, most of whom were apparently healthy and well and had never had diphtheria or received an injection of diphtheria antitoxin. A few were convalescent from scarlet fever or suffering with various chronic ailments and were tested while undergoing observation and treatment in the wards of various hospitals in Philadelphia. The results are summarized in Table 1.

TABLE 1.—The Diphtherin and Toxin Skin Reactions in Persons of Various Ages

Age, Years	Total Tested	Diphtherin Reactions			Toxin Reactions		
		Positive	Negative	Per Cent. Positive	Positive	Negative	Per Cent. Negative
Under 1	17	15	2	88	3	14	82
1 to 4	41	29	12	70	23	18	44
4 to 8	23	17	6	73	12	11	47
8 to 12	10	7	3	70	3	7	70
12 to 20	10	3	7	30	2	8	80
Over 20	87	40	47	45	33	54	62
Total	188	111	77	..	76	112	

As a negative toxin and a positive diphtherin reaction are regarded as indicating the presence of an antitoxic and anaphylactic antibody, respectively, the percentage of negative toxin and positive diphtherin reactions are given.

As shown in Table 1, a surprisingly large percentage of persons reacted in a positive manner to the diphtherin test. The majority of these reactions were of papular variety.

The larger percentage of positive anaphylactic reactions observed with diphtherin than with the protein contained in the dose of toxin used in the Schick test is to be expected on account of the larger amount of diphtheria protein injected. Thus the protein in the toxin test may produce about 30 to 35 per cent. anaphylactic reactions, while the percentage of reactions to diphtherin is much higher.

Children under 1 year of age showed the highest percentage of positive diphtherin reactions, 88 per cent.; among children from 1 to 12 years of age positive reactions were observed in about 70 per cent. Adults were found to react less frequently, about 75 per cent. of reactions being positive. Very young and poorly nourished infants usually fail to react in a definite manner, although small and poorly defined areas of erythema and edema may be detected. The results of the toxin tests were closely similar to those found in our previous work.

Both antibodies, namely, antitoxin and anaphylactic antibodies, were found in highest percentage among children under 1 year of age; after that age the percentage of persons showing anaphylactic antibodies gradually decreased, the lowest percentage of positive diphtherin reactions being found among adolescents and adults. Antitoxic immunity (negative Schick tests), on the other hand, has been generally found in from 65 to 90 per cent. of persons over 15 years of age.

The largest percentage of persons were found to react positively to the diphtherin and negatively to the toxin tests, indicating the presence of anaphylactic and antitoxic antibodies; some reacted negatively to the diphtherin and positively to the toxin tests, indicating the absence of both antibodies; others were positive (anaphylactic antibodies present and antitoxin absent) or negative (anaphylactic antibodies absent and antitoxin present) to both. The results among 188 persons were as follows:

1. Those reacting positively in the diphtherin and negatively in the toxin tests were 53.3 per cent.

2. Those reacting negatively in the diphtherin and positively in the toxin tests were 10 per cent.

3. Those reacting positively in both tests were 12.5 per cent.

4. Those reacting negatively in both tests were 24.1 per cent.

In other words, the serums of about 50 per cent. of persons contain both natural antitoxic and anaphylactic antibodies; only 10 per cent. of persons were found to contain neither of these antibodies. About 24 per cent. of persons showed the presence of antitoxic and absence of anaphylactic antibodies and only 12.5 per cent. the presence of anaphylactic and the absence of antitoxic antibodies.

If a positive diphtherin reaction may be interpreted as indicating a condition of lytic immunity, as a negative toxin test of Schick is regarded as indicating an antitoxic immunity, it is to be noted that the diphtherin test agreed with the toxin test in 63 per cent. of cases. In 37 per cent. of persons the results differ, and largely (24 per cent.) to the effect that persons may possess natural antitoxin, and thereby yield negative toxin reactions, but with no anaphylactic antibodies, and thereby yield negative diphtherin reactions.

If immunization with diphtheria antitoxin were guided by the results of these tests, the diphtherin test would reduce the number of persons requiring passive immunization by about 12 per cent., as this percentage was found to yield positive allergic reactions and the blood serums no antitoxin.

THE DIPHTHERIN REACTION AMONG PERSONS WHO HAD RECEIVED DIPHTHERIA ANTITOXIN

We have applied the diphtherin and toxin tests to sixty-one children receiving curative or prophylactic doses of diphtheria antitoxin with the result shown in Tables 2 and 3.

No opportunities were afforded for applying the tests to persons having diphtheria, or to those recovering from the disease, who had not received antitoxin.

TABLE 2.—The Diphtherin and Toxin Skin Reactions Among Persons Suffering with Diphtheria and Receiving Antitoxin

Number	Age, Years	Diagnosis	Antitoxin Units	Days after Antitoxin	Reactions	
					Diphtherin, Cm.	Toxin, Cm.
1	11	Tonsillar diphtheria.....	12,000	8	1.5 × 1.5	1 × 1
2	11	Tonsillar diphtheria.....	20,000	11	1 × 1	—
3	3	Tonsillar diphtheria.....	15.000	12	—	—
4	4	Tonsillar diphtheria.....	50,000	14	—	—
5	3	Tonsillar diphtheria.....	12,000	15	0.6 × 0.0	—
6	3	Tonsillar diphtheria.....	12,000	15	0.6 × 0.6	—
7	8	Tonsillar diphtheria.....	5,000	15	2 × 2.5	1 × 1.5
8	7	Laryngeal diphtheria.....	20,000	17	—	—
9	3	Tonsillar diphtheria.....	15,000	17	1 × 1	—
10	5	Laryngeal diphtheria.....	25,000	18	1 × 1	—
11	3	Laryngeal diphtheria.....	15,000	18	0.6 × 0.6	—
12	8	Tonsillar diphtheria.....	30,000	19	1 × 1.05	—
13	5	Tonsillar diphtheria.....	20,000	18	0.6 × 0.6	—
14	8	Positive culture case.....	8,000	20	1.5 × 1.5	1.5 × 1.5
15	4	Tonsillar diphtheria.....	30,000	22	1 × 0.7	—
16	3	Tonsillar diphtheria.....	20,000	22	1 × 1	—
17	11	Laryngeal diphtheria.....	17,000	26	1 × 1	—
18	8	Tonsillar diphtheria.....	30,000	28	1 × 0.6	—
19	3	Tonsillar diphtheria.....	15,000	30	0.6 × 0.6	—
20	5	Tonsillar diphtheria.....	20,000	31	—	0.4 × 0.8
21	2	Tonsillar diphtheria.....	35,000	31	—	—
22	2	Tonsillar diphtheria.....	15,000	31	0.6 × 1	—
23	3	Tonsillar diphtheria.....	10,000	37	0.6 × 1	0.5 × 0.5
24	9	Tonsillar diphtheria.....	30,000	47	1.5 × 1.5	—
25	7	Nasal diphtheria.....	60,000	48	1 × 1	—
26	3	Nasal diphtheria.....	35,000	45	1 × 1	1 × 1
27	11	Tonsillar diphtheria.....	60,000	54	0.6 × 0.6	—
28	9	Nasal diphtheria.....	20,000	61	1.2 × 1.5	—

As shown in Table 2, about 82 per cent. of children convalescent from diphtheria after receiving large injections of immune antitoxin reacted positively to the diphtherin test; this proportion of positive reactions was about 10 per cent. higher than found among normal children of the same age and probably indicates the development of sensitization to diphtheria protein among these infected individuals.

As shown in Table 3, the prophylactic administration of antitoxin to thirty-three normal children did not influence the percentage of positive diphtherin reactions as tested at the intervals indicated.

TABLE 3.—The Diphtherin and Toxin Skin Reactions in Children Who Had Received 1,250 Units of Antitoxin

Number	Age, Years	Days after Antitoxin	Reactions	
			Diphtherin, Gm.	Toxin, Gm.
1	3	7	—	—
2	5	10	1 × 1	1 × 1
3	2	10	—	—
4	7	11	0.6 × 1	—
5	4	15	—	0.5 × 0.5
6	1	19	0.6 × 1	—
7	7 mos.	23	1 × 1	—
8	9	25	—	—
9	11	28	—	0.6 × 0.6
10	8 mos.	36	—	—
11	9	37	0.5 × 0.5	—
12	7	48	—	—
13	1½	60	—	1 × 1
14	6	72	1 × 1	—
15	6½	72	—	—
16	3	72	0.6 × 0.6	—
17	7	72	1 × 0.6	—
18	6	72	1 × 0.8	0.6 × 0.6
19	5	72	0.6 × 0.6	—
20	5	72	1 × 1	1 × 0.4
21	4	72	—	—
22	8	72	1 × 1	—
23	9	72	1 × 1	0.5 × 0.5
24	8	72	1 × 1.2	—
25	5	72	1 × 1.5	—
26	2½	72	—	—
27	2	72	0.6 × 0.6	1 × 0.6
28	5	72	—	—
29	2	90	—	—
30	9	90	1 × 1.2	1 × 1
31	6	95	—	—
32	3	120	—	—
33	3	120	1 × 1	1 × 1

DIPHTHERIA BACILLUS CARRIERS AND THE DIPHTHERIN REACTION

As reported in our previous paper, we have found no relation between the Schick toxin reaction and the percentage of diphtheria bacilli carriers. Persons may carry virulent bacilli in the upper air passages and react negatively to the toxin test, the absence of both symptoms of intoxication and local skin reactions being due apparently to the presence of natural antitoxin. Large numbers of carriers have been found who reacted positively to the toxin skin test, but the bacilli proved nonvirulent for guinea-pigs. As shown by Park, however, the Schick test possesses some diagnostic value in a negative way for diphtheria, in that a person presenting certain symptoms, such as a dirty nasal discharge, who reacts negatively to the skin test, may be excluded on the basis that antitoxin in the blood serum sufficient to effect neutralization of the test toxin will protect the individual against diphtheria toxin; on the other hand, a positive reaction indicates that diphtheria may be present, on the basis that the person is shown to be at least susceptible to the toxin.

Similar results were observed with the diphtherin reaction. During this study, cultures were made of the throats of 124 and the noses of twenty-seven persons, in whom both the diphtherin and toxin tests were made, with the following results:

1. Of twenty-six persons convalescent from diphtheria and harboring bacilli virulent for guinea-pigs in the throat, twenty, or 80 per cent., reacted positively to the diphtherin test and twenty-two, or 84 per cent., negatively to the toxin test. In all but one instance the positive toxin tests occurred among persons showing positive diphtherin reactions.

2. The results of the remainder of these tests are summarized in Table 4. None of these cultures was tested for virulence; the majority were of the long and solid types of diphtheria bacilli. The throats of all persons appeared normal, although many of the children had rhinitis, with discharges of varying degrees of severity.

TABLE 4.—THE RESULTS OF CULTURES OF THE NOSES AND THROATS AND OF THE DIPHTHERIN AND TOXIN TESTS

Culture from	Total	Results of Culture	Diphtherin Test		Toxin Test	
			+	−	+	−
Throat	19	Positive	9	10	6	13
Throat	105	Negative	70	35	32	73
Nose	17	Positive	10	7	7	10
Nose	10	Negative	7	2	2	8

It is apparent that there is no relation between the occurrence of the diphtherin reaction and the presence of diphtheria bacilli on the mucous membrane of the upper respiratory tract. If these reactions to diphtherin may be interpreted as indicating sensitization to the diphtheria protein, it is possible that sensitization had occurred at a previous time when the mucous membranes harbored the bacilli, or the condition may apparently be acquired by inheritance, the problem being as difficult and indefinite as that surrounding the question why certain persons possess natural diphtheria antitoxin while others do not.

Persons may harbor virulent toxin-producing bacilli and show no evidences of toxemia and react in a negative manner in the toxin test. Their immunity is evidently antitoxic, and while they are not infected in the sense of showing the clinical evidences of diphtheria, they are carriers of dangerous bacilli and may truly be regarded as infected individuals. In this manner the physician may be misled by a negative Schick reaction; the evidence of the test may be taken as an indication that the administration of antitoxin is not required, but nothing more; the question of quarantine because of the possibility of such a person being a carrier of dangerous bacilli must be decided by bacteriologic examination, and preferably by animal inoculation tests.

CLINICAL SIGNIFICANCE OF THE DIPHTHERIN REACTION

If there was sufficient experimental evidence to the effect that cutaneous anaphylactic reactions may be taken as an index to immunity, on the basis that the same or similar antibodies that are capable of reacting with the protein of the dead bacilli may attack the protein and destroy the living bacilli, the diphtherin reaction might prove of some value in the practical management of diphtheria, on the assumption that a person may be protected by the presence of an antibody other than antitoxin.

I have continued this work to determine this point more specifically, in so far as the question can be answered by tests in vitro for bactericidal and other antibodies, the results being given in a separate communication;[4] here it may be stated that the results of these investigations have shown that there is absolutely no relation between the skin reaction and the presence or absence of bacteriolysin and antitoxin for the diphtheria bacillus and its toxins in the body fluids. As far as I am able to determine experimentally, the diphtherin test shows that a person is or is not hypersensitive or anaphylactic to the diphtheria protein, and the chief clinical significance of this reaction consists almost solely in the fact that these reactions, when occurring during the application of the Schick test, may be regarded as positive toxin

4. Kolmer, J. A.: The Diphtherin Skin Reaction in Relation to Immunity in Diphtheria, Journal of Immunology.

reactions and accordingly followed by needless attempts at passive or active immunization. My experiments show that immunity in diphtheria is practically solely antitoxic in character, and the Schick test appears to fulfil the requirements of a practical test for immunity to this infection.

Furthermore, as indicating the absence of any relation between the anaphylactic diphtherin test and resistance in diphtheria, I have seen three persons yielding positive diphtherin reactions contract diphtheria; all of these had likewise yielded positive toxin reactions, indicating thereby an absence of sufficient natural antitoxin to confer immunity to this infection.

As far as I am aware, the chief practical value of the diphtherin reaction, entirely aside from its theoretical and academic interest, is as a control on the Schick test to detect and differentiate the anaphylactic from the true toxin reaction.[5]

CONCLUSIONS

1. Following the injection of diphtheria toxin in the conduct of the Schick test for antitoxic immunity in diphtheria, inflammatory reactions may be produced (1) by trauma and undue sensitiveness of the skin; the influence of these reactions may be minimized by injecting a minimum quantity of fluid (not over 0.1 c.c.); by using a stock toxin of high potency in order to require high dilution and the consequent injection of a minimum amount of the constituents of the broth, and by the employment of a proper technic (especially a small needle); (2) by an anaphylactic reaction to the protein of the diphtheria bacillus and to a lesser extent to the protein constituents of the broth itself, the former being more important; (3) by the irritating effects of the toxin itself, constituting the true toxin reaction of Schick.

2. An anaphylactic skin reaction to the protein of the diphtheria bacillus was observed in about 70 per cent. of children and 35 per cent. of adults following the intracutaneous injection of a polyvalent antigen of washed, neutralized and heat-killed diphtheria bacilli (diphtherin).

3. These reactions were regarded as anaphylactic in character and therefore entirely distinct from the true toxin reaction of Schick.

4. The percentage of positive diphtherin reactions was higher than the anaphylactic reactions observed with the toxin of the Schick test due to a higher amount of protein being injected.

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5. Lately Zingher (The Pseudoreaction in the Schick Test and Its Control, Jour. Am. Med. Assn., 1916, lxvi, 1617) has advocated for this purpose the injection of a toxin heated at 75 C. for five minutes to destroy the toxin or one overneutralized with antitoxin. I have tried both methods and am ready to subscribe to the value of the former as fulfilling all the requirements for detecting the anaphylactic state under conditions governing the conduct of the toxin test.

5. About 53 per cent. of persons of various ages yielded positive diphtherin and negative toxin (Schick) reactions. About 10 per cent. yielded negative diphtherin and positive toxin reactions, both tests agreeing therefore in about 63 per cent. of persons; 12.5 per cent. reacted positively and 24.1 per cent. negatively to both tests.

6. The percentage of positive diphtherin reactions was slightly greater among those who were convalescent from diphtheria.

7. There is no relation between the occurrence of positive and negative diphtherin and toxin reactions and the presence or absence of diphtheria bacilli in the upper air passages. A negative toxin reaction (Schick) in a person presenting clinical evidences of infection indicates that the individual does not require antitoxin, but nothing more; he may be infected with virulent diphtheria bacilli capable of disseminating the disease.

8. While the diphtherin test indicates hypersensitiveness to the protein of the diphtheria bacillus, it has probably no value as an index of immunity and is of practical interest mainly from the viewpoint that the anaphylactic reaction may be mistaken for a positive Schick reaction.

CLINICAL DEPARTMENT

SARCOMA OF THE KIDNEY TREATED BY THE ROENTGEN RAY*

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It is generally accepted as axiomatic that the only hope in cases of sarcoma of the kidney in childhood lies in early nephrectomy. Even under this procedure the mortality is very high on account of the likelihood of metastases, although the operation itself may be well borne.

The following case is reported because the growth was so large that no surgeon was willing to undertake its removal. For this reason recourse was had to treatment by the Roentgen ray. For a time there was marked improvement. The tumor became much smaller in size, and the child gained in weight and strength. After a time, however, the tumor began to increase in size again. Later, the child contracted measles, with complicating bronchopneumonia. At necropsy the actual results of the Roentgen ray treatment on the tumor mass could be studied. The report herewith submitted is presented because of the opportunity offered to study the effects of intensive Roentgen-ray treatment in a case of this sort.

W. S., boy, white, aged 4 years, was admitted to the pediatric service of the Cincinnati General Hospital on Oct. 20, 1915. The history was one of increasing languor and lassitude, with loss of appetite and anemia. The mother had noticed a mass in the abdomen three months before the child was brought to the hospital. A physician outside had suggested Roentgen-ray treatments. Two of these were given by a roentgenologist. After each of these treatments the boy vomited and passed almost pure blood for a day. This statement by the mother was later confirmed by the roentgenologist himself. For a time after the treatments the boy seemed better, but the improvement did not last.

On examination the child was found to be poorly nourished. Except for the condition of the abdomen, the physical findings were not of moment.

The entire left abdomen was filled by a tumor mass, extending from the costal margin in the nipple line to 3 cm. above the symphysis. The tumor extended 1 cm. to the left of the umbilicus. It was hard, distinctly nodular, apparently not tender to pressure and could be moved forward by pressure from behind.

Uranalysis on admission showed distinct microscopic hematuria. The blood showed a secondary anemia. Fluoroscopic examination with colon partly filled with gas showed a sharply defined dark shadow in the region normally occupied by the kidney. Roentgen-ray plate of the lungs for the characteristic metastatic sarcomatous shadows was negative.

* Submitted for publication May 21, 1916.

In view of the fact that all of the surgeons who saw the child advised against operation because of the apparent hopelessness of the case, Roentgen-ray treatments were instituted.

Treatments were given with the Coolidge tube. Three areas, front, back and side of the tumor, were covered at each treatment, except the first and second, when one and two areas, respectively, were treated. Twenty treatments were given at intervals of about a week, with a dosage as indicated in the table. The distance in all treatments was 8 inches, with a spark gap of 9 inches.

TABLE 1.—DOSAGE EMPLOYED IN ROENTGEN-RAY TREATMENTS

Date	Ma. Seconds
1915—	
Oct. 30	10
Nov. 5	15
Nov. 9	15
Nov. 15	20
Nov. 23	25
Dec. 1	25
Dec. 8	25
Dec. 15	25
Dec. 24	25
Dec. 29	25
1916—	
Jan. 4	25
Jan. 12	25
Jan. 19	25
Jan. 26	25
Feb. 5	25
Feb. 12	25
Feb. 21	25
March 3	50
March 10	50
March 17	50

Before each Roentgen-ray treatment the child was given full doses of potassium citrate for a day. As a result of this alkalinization, no Roentgen-ray toxemia followed any of the treatments, except the last. Neither was there any increase of the blood in the urine after the treatments.

After the seventh treatment, given on December 8, it was noted that the tumor had decreased very markedly in size. The child had gained several pounds in weight, looked rosy and well and played like an apparently normal child. In January the child had an attack of influenza, then epidemic in the wards, with double otitis media. The recovery was prompt. By March 1 the child was again very listless and apathetic. The tumor had grown appreciably in size. On March 30 the boy came down with measles, and death occurred on April 4.

The necropsy showed a sarcoma of the left kidney with small metastasis in both lungs and in the liver. The complete pathologic report is not given here.

At my request Prof. P. G. Woolley, pathologist to the hospital, made a microscopic examination of the tumor itself, with reference to the effects of the Roentgen ray on the growth. His report is herewith submitted:

Specimens for microscopic examination were removed from five different points in the tumor, one from near the upper pole, one from near the lower

pole, one from the middle of the tumor at the edge of a hemorrhagic area, and the other two from intermediate portions. The capsule of the tumor was thick and hyaline like that seen in *Zuckergussleber*.

The stained sections showed the most widespread and generally diffuse necrotic changes, with no evidence of inflammatory reaction. Even the stroma showed degenerative changes, associated with irregular areas of edema. The parenchyma was almost completely necrotic, and, except in a few areas, chiefly near the lower pole, showed almost no evidence of structure. One could discern the remains of stroma and parenchyma, by means of the staining reactions, but all histologic cellular structures were lost. Karyorrhexis and karyolysis were obvious and the general appearances suggested those seen in areas of diffuse caseation. The capsule of the whole tumor mass was, on the other hand, hyaline, and, especially about the blood vessels, showed the structure of hyaline connective tissue. At no place was there any evidence of malignant cellular infiltration.

In the areas where some tumor structure persisted, the appearances were those of an alveolar sarcoma, and in these areas short spindle cells and round cells were present, chiefly the latter. In these areas the capillary vessels were healthy. About the margins of these tumorous foci the tumor cells and the interstitial cells were both changed. The former showed, first, pyknosis, and, as the areas of complete degeneration were approached, rhexis and swelling; the latter, edema and vacuolization.

The fact that the whole necrotic process was so widespread in such a large tumor mass; that there was no evidence of vascular thrombosis in the main vessels and no evidence of infarction; and that the degenerative process appeared to be a gradually progressive one, indicates that the Roentgen-ray treatments were at least partially the cause of the retrogression.

In view of some recently reported cases of hypernephromas of the kidney cured by the Roentgen ray it has seemed worth while to put on record this failure of the treatment in a sarcoma of the kidney in childhood.

Yet it should not be forgotten that the case was a particularly unfavorable one. Unquestionably, when a nephrectomy can be done with any prospect of success, it should be the procedure of choice. But it must be remembered that the mortality under surgical procedure is very high.

In view of the changes effected in the tumor mass by the Roentgen ray in this case (and the fact being admitted that one case does not permit the drawing of any sweeping conclusions), it seems justifiable to say that if nephrectomy is contraindicated in a case of sarcoma of the kidney, the Roentgen ray should be given a thorough trial.

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